

**Pathogens in an anthropized world: a geographical perspective on zoonotic and vector-borne diseases**

**Pathogènes dans un monde anthropisé: une perspective géographique sur les zoonoses et maladies à transmission vectorielle**

**Pathogenen in een geanthropiseerde wereld: een geografisch perspectief op zoönoses en vector-overgedragen ziekten**

Sophie O. Vanwambeke\*

\*corresponding author; Université catholique de Louvain, Earth & Life Institute, Georges Lemaître Centre for Earth and Climate Research.

Place Pasteur 3, 1348 Louvain-la-Neuve, Belgium

Tel. : +32(0)10472871 ; Fax : +32(0)10472877

sophie.vanwambeke@uclouvain.be

### **Keywords**

Medical geography, *Aedes*-borne virus, biological resources, environmental factors, human environment interactions

## Abstract

Infectious diseases have not been relegated to humankind's past, far from it. This is being strikingly illustrated by the ongoing Zika fever epidemic in South America. While interest for the links between infectious diseases and the environment, in particular for vector-borne and zoonotic diseases, has drawn the attention of scientists from various disciplines for a long time, the currently exploding data availability and modeling capacity are opening new avenues for a better understanding and prediction of such infections. We present a resource-based habitat concept, expanded to include human populations, as a framework for unifying knowledge and research in the field of vector-borne diseases, with a focus on *Aedes*-borne viruses such as Zika virus and dengue virus.

Les maladies infectieuses n'ont pas été reléguées dans le passé de l'humanité, loin s'en faut. Ceci est illustré de manière frappante par l'épidémie de fièvre Zika en cours en Amérique du Sud. Les liens existants entre les maladies infectieuses, en particulier les zoonoses et maladies transmises par les vecteurs, et l'environnement ont attirés l'attention des scientifiques de disciplines variées depuis longtemps. Aujourd'hui toutefois, l'explosion de la disponibilité des données et les possibilités offertes par la modélisation ouvrent de nouvelles avenues pour une meilleure compréhension de telles infections. Nous présentons ici un cadre conceptuel d'habitat basé sur les ressources, élargi pour inclure la population humaine. Ceci offre un cadre pour assembler les connaissances et la recherche dans le domaine des maladies à vecteur. Nous nous focalisons ici sur les virus transmis par les moustiques du genre *Aedes*, tels que le virus Zika et la virus de la dengue.

Infectieziekten behoren jammer genoeg niet enkel tot het verleden. Dit wordt levendig geïllustreerd door de recente uitbraak van Zika koorts die zich momenteel voltrekt in Zuid-Amerika. De verbanden die bestaan tussen besmettelijke ziekten, zoönoses en vector-overgedragen ziekten enerzijds, en omgevingsfactoren anderzijds, hebben al sinds lang de aandacht getrokken van wetenschappers uit diverse disciplines. Vandaag de dag stellen de enorme hoeveelheden aan gegevens alsook simulatiemodellen ons in staat om nieuwe pistes te verkennen die ons een beter inzicht kunnen geven in infectieziekten.

We presenteren hier een conceptueel kader voor de studie van habitats dat uitgaat van bestaansmiddelen en dat op een expliciete manier de menselijke bevolking in rekening neemt. Deze benadering biedt een uniek framework om onze kennis van vector-overgedragen ziekten te vergroten. In deze paper richten we ons op de virussen die worden overgedragen door *Aedes* muggen, zoals het Zika virus and dengue virus.

## *Introduction*

News over the past few years have reminded us that, far from being in our past, infectious diseases are persisting and will persist. Infectious diseases were, and will be, companions of humankind (Fauci and Morens, 2012; Jones et al., 2008). Most recently headlining the news is the mosquito-borne Zika fever, caused by Zika virus. After emerging in the Pacific in 2007, its first appearance in America has been identified, retrospectively, in Brazil in late 2014 (Musso and Gubler, 2016). It is now estimated to have caused about 30000 cases in Brazil (Faria et al., 2016). Known to virologists since its discovery in the Zika forest of Uganda in 1947, Zika virus had previously been recorded in Africa and Asia (Fauci and Morens, 2016). Infection with Zika virus had been associated generally with mild, self-limiting symptoms prior to 2013, but this changed following the French Polynesia epidemic. Strong hypotheses exist concerning neurological complications (Guillain-Barré syndrome) (Musso and Gubler, 2016) and neurological complication in neonates (microcephaly) (Cauchemez et al., 2016; Johansson et al., 2016). While still incomplete, the epidemiological and experimental evidence for the link between microcephaly and infection with Zika virus is mounting fast enough for the WHO to have declared an emergency on the 1<sup>st</sup> of February 2016 (World Health Organisation, 2016), and for the CDC to recommend that pregnant women avoid travelling to areas where the virus is known to circulate (Center for Disease Control, 2016). All ingredients for widespread worry amongst the general population, and for major global concern are gathered: a virus likely to cause severe birth defect emerging on a continent where it was previously unrecorded, transmitted by mosquitoes that are at the moment expanding their distribution globally on a backdrop of global environmental change. In the meantime, dengue persists as a scourge of the tropics, causing an estimated 390 million infections and 96 million symptomatic cases yearly (Bhatt et al., 2013).

Being mosquito-borne, arboviruses such as dengue virus and Zika virus have strong relationships with the environment: their transmission cycle relies on exothermic vectors, and, often, wild reservoir hosts. All these organisms have specific habitat requirements that environmental conditions affect. The idea that mosquito-borne diseases, and more generally, vector-borne diseases, are tightly associated to environmental conditions is not novel, and has been formulated in diverse fields such as medicine, by e.g. Jacques May (May, 1952), biogeography, by e.g. Eugene Pavlovski (Pavlovsky, 1966), and geography, by e.g. Maximilien Sorre in France (Sorre, 1933). Their studies looked closely at various vector and pathogen systems and established the foundations of what can now be found under the broad field of landscape epidemiology. In geography, work has expanded greatly in the second half of the 20<sup>th</sup> century, applying emerging quantitative methods and dealing with diverse topics ranging from AIDS to health care (Verhasselt, 1993).

Interest for the connections between vector population distribution, pathogen circulation, and the environment has however soared in the past twenty years (Kitron, 1998; Ostfeld et al., 2005; Reisen, 2010), and two major reasons can be highlighted for this. First, as emphasized by recent epidemics, many aspects of ongoing global environmental changes have a significant impact on the risk of infectious disease emergence and re-emergence. This goes clearly well beyond the climatic aspects of global change (Jones et al., 2013; McMichael, 2004). Changes in animal populations (domestic and wild), in human populations, in interactions between animal and human populations, land use and cover change, global travel of goods and people, all have been related to notable events related to infectious diseases. Second, our capacity to analyze the associations between environmental and epidemiological factors is greater than ever. Key to this is the data availability: we can now map with

high spatial and temporal resolution many environmental factors relevant to zoonotic and vector-borne diseases (Estrada-Peña et al., 2016; Herbreteau et al., 2007; Rogers et al., 2002). The efforts allocated to monitor and model the global environment and its changes are benefitting efforts to better understand and predict the distribution and dynamics of vectors and vector-borne diseases. Data concerning vectors, pathogens, and diseases are also getting more widely available thanks to increase in reporting, better data publication and compilation (Purse and Golding, 2015), as well as the appearance of novel digital tools (Madder et al., 2012) and citizen science projects (Garcia-Martí et al., 2016). These data can be fed to ever more elaborate yet more accessible models of the effect of the environment on vector distribution, pathogen distribution, and disease risk (e.g. Cianci et al., 2015; De Clercq et al., 2015). Expanding data and model elaboration together offer a world of possibilities as well as needs. Despite this broad availability, the data often represent keyholes onto complex ecological systems. Environmental data are often proxies of the actual factors considered (Estrada-Peña et al., 2016), and most epidemiological data only ever monitors a part of the transmission system (Randolph, 2001). This results in a plethora of results that are incomparable, either because proxies are not directly comparable, because the part of the transmission system is different, or because the spatial or temporal scales considered differ. We propose that a strong conceptual background focused on the ecology of the pathogen would help consolidating knowledge already acquired in previous modeling efforts, and elaborate more coherent models even if they answer diverse needs.

In this paper we elaborate a resource-based habitat concept as drawn from conservation ecology, focused on the case of *Aedes*-borne flaviviruses such as Zika virus and dengue virus, two viruses of global public health concern. We detail the concept as adapted to such pathogens, all the way to their human niche, then discuss how it could help identifying and formulating ecological hypothesis, and guide modeling and monitoring efforts.

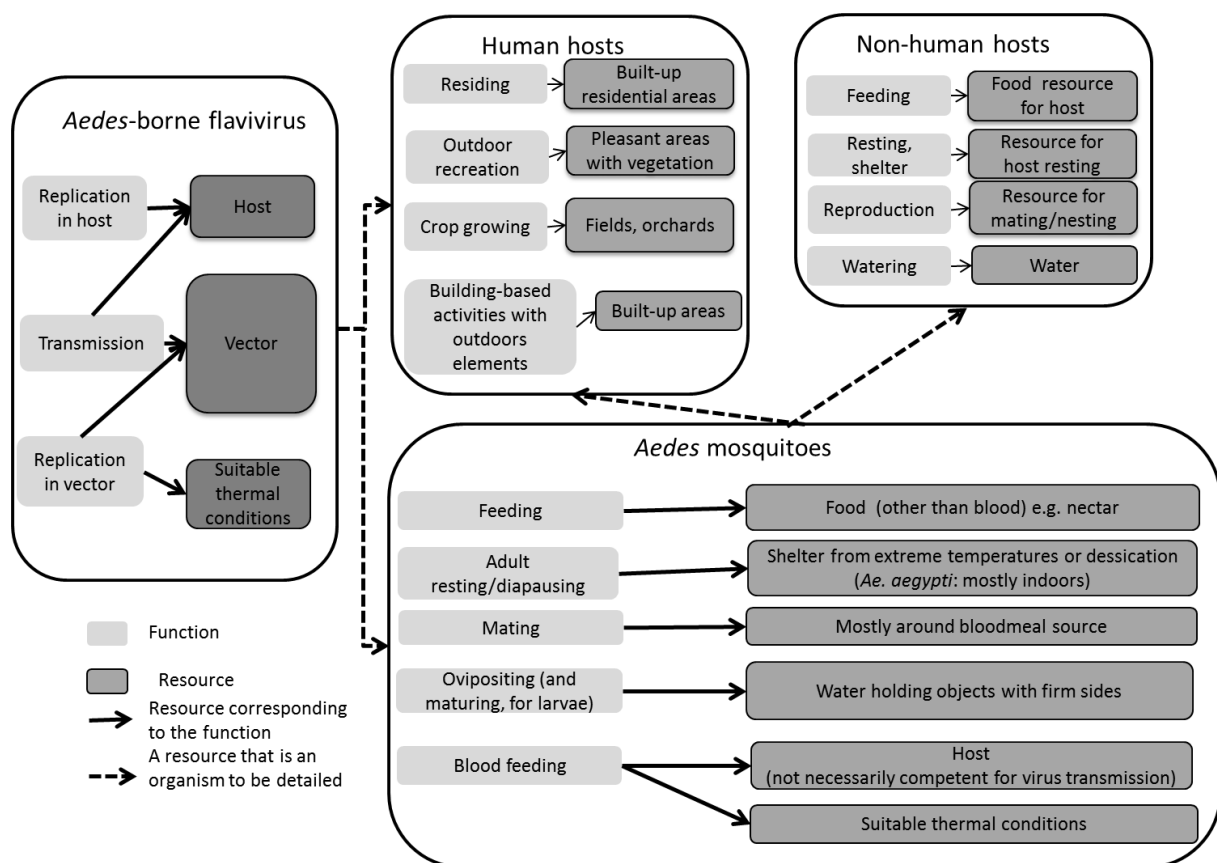
#### *Pathogens as organism of focus : Aedes-borne flaviviruses*

As we will see, our proposed resource-based habitat concept focuses ultimately on the pathogen. In this paper, we focus on two *Aedes*-borne flaviviruses of public health importance: Zika virus and dengue virus. Other *Aedes*- or mosquito-borne flaviviruses include Yellow Fever virus, West Nile virus and Japanese encephalitis virus (Grard et al., 2010). Dengue virus usually causes asymptomatic or mildly symptomatic disease, but can cause dengue hemorrhagic fever. Dengue fever is found across the tropics, but incidence is difficult to estimate as most cases present mild symptoms. The WHO estimates that dengue fever causes about 50 to 100 million cases annually (Special Programme for Research and Training in Tropical Diseases and World Health Organization, 2009) but others place this figure at about 90 million (Bhatt et al., 2013). Both viruses appear to be principally vectored by *Aedes aegypti* and *Aedes albopictus* mosquitoes. These two species are extremely well adapted to anthropized landscapes.

Dengue virus and Zika virus transmission relies on at least three species (pathogen, vector, and host). Often, both *Ae. aegypti* and *Ae. albopictus* are implicated in transmission. When sylvatic transmission is taking place, involving non-human primates and monkeys, several host species also need to be considered. This means that examining the ecological functions and resources required for the various species involved in transmission will be necessary to represent the habitat of the virus. It also means that most monitoring efforts will only document a section of the transmission cycle.

#### *A resource-based habitat for Aedes-borne flaviviruses*

The resource-based habitat concept (RBHC) finds its origin in conservation ecology primarily (Hartemink et al., 2015) and adopts a functional ecology perspective, with a focus on the organism and its needs, rather than on habitat characteristics such as vegetation classes (Dennis et al., 2006, 2003). The functions that the organism of focus – here, the pathogen – need to carry out are identified (e.g. feeding, mating, oviposition,...). These functions are then associated to specific resources found in the environment. The resources can be either a consumable (e.g. host plant for an herbivorous insect), or utility (e.g. suitable micro-climate). A bottom-up approach is thus adopted here, in line with the classical ecological niche concept. Furthermore, the resource-based habitat concept explicitly accounts for the movement capacity of the organism, thus, its capacity to make use of diverse, multiple resources in the landscape, provided they are within reach. Contrary to a habitat-focused approach, that often tends to associate a single land cover class to an organism, combinations of landscape elements or land cover types that offer all the required resources can be identified and mapped (Hartemink et al., 2015). Here we bring this ecological perspective towards the geographical perspective by including human hosts and their own relevant functions and resources. We focus here on fine-scale environmental features and ecological interactions at the landscape level, and assume climatic conditions favorable to pathogen, vectors, and hosts.



## 1. Pathogen level

We can identify three essential functions for *Aedes*-borne flaviviruses: replication in the host, replication in the vector, and transmission. This leads us to identify two resources necessary for

the pathogen: vectors and hosts. Vectors are here identified as mosquitoes of the genus *Aedes*, and we focus here on the two species of primary interest for public health: *Ae. aegypti* and *Ae. albopictus*. The host species of interest will vary according to whether the virus considered circulates in non-human hosts in a sylvatic cycle, or whether the virus has adapted to circulate, at least in part, in humans.

## 2. Vector level

Vectors are a necessary resource for the pathogen functions of transmission and replication in the vector. They have of course their own functions and resources that need to be accounted for, which include hosts. For *Aedes* mosquitoes, we can identify the functions of (Figure 1): feeding, adult resting and diapausing, mating, ovipositing (and maturing, for larvae), and blood feeding. Feeding here refers to nectar feeding, which requires plant, either nectar or honeydew, possibly also from fruits and sap from wounds. The importance of this varies between males and females (Stone and Foster, 2013), as only females feed on blood. The importance of nectar feeding for females appears to vary between sites, possibly in relation to availability, and may affect vectorial capacity. *Ae. aegypti* females, highly adapted to the human indoor environment, largely rely on multiple blood feeding to get energy (Scott and Takken, 2012). For *Ae. aegypti*, resting largely relies on the human built-up environment, with a strong preference for those buildings where humans are found (Ritchie, 2014). In *Aedes* mosquitoes, mating does not necessarily take place in swarms, as males usually seek females around blood meal sources (Oliva et al., 2014). Oviposition takes place in water-holding objects with firm sides (Ritchie, 2014). This includes artificial containers made out of a diversity of materials, as well as some natural containers such as tree holes, bamboo, open coconuts, leaves. *Ae. aegypti*, now fully adapted to the urban environment, relies mostly on artificial containers (Ritchie, 2014), while *Ae. albopictus* relies on both artificial and natural containers (Vanwambeke et al., 2007). Such objects suitable for *Aedes* breeding can also be found in cultivated areas such as orchards (Vanwambeke et al., 2007), so their role as an area providing ovipositing resources may need to be considered. These mosquito species may have adapted to artificial containers as early as the 17<sup>th</sup> century in the case of *Ae. aegypti*. This has allowed them to travel from continent to continent, during the slave trade for *Ae. aegypti* (Gubler, 2014), and more recently with trade of goods for *Ae. albopictus* (Kraemer et al., 2015; Reiter and Sprenger, 1987). Blood feeding resources, i.e. hosts, are essentially found in humans for *Ae. aegypti*, emphasizing its current full reliance on the anthropized environment as highlighted for ovipositing sites. While *Ae. albopictus* is known to be more opportunistic (Paupy et al., 2009), if humans are available it will largely feed on them, or on animals associated to humans such as dogs and pigs (Ponlawat and Harrington, 2005). Possibly a better way to describe the feeding behavior of *Aedes* mosquitoes is their plasticity in relation to circumstances (Faraji et al., 2014).

## 3. Host level: non-human hosts

In the case of the viruses of focus here, non-human hosts do not always intervene. Dengue virus mostly circulates as an urban, entirely human transmission cycle. In Asia, where dengue virus originates, all four dengue virus serotypes have been identified in sylvatic cycles, that is a transmission cycle relying on non-human primates and monkeys (Gubler, 2014). The move out of the forest and into rural villages is estimated to have taken place about 2000-4000 years ago (Gubler, 2014). When these viruses are introduced into new areas, it is most importantly related

to the travel of infected humans bringing the virus into a new area (e.g. for Zika: Faria et al., 2016; Musso and Gubler, 2016). However the role of non-human hosts may be significant in those areas where an urban cycle is not established yet or where control efforts are reducing virus circulation in humans. The current epidemic of Zika fever in Brazil illustrates these issues. Preliminary results indicate that the virus may circulate in non-human primates (Favoretto et al., 2016). In circumstances where possible non-human hosts are found, it may be useful to include them. Because focusing on a specific species is not relevant here, we do not detail the functions and associated resources beyond the general indications of Figure 1.

#### 4. Host level: human hosts

A full list of functions of human hosts would be challenging, but is not necessary. Only those functions or human activities that may expose them to mosquito bites, thus exposing them to be infected, or to serve as a host and infect mosquitoes, need to be pinpointed. Indeed, this may still include a broad diversity of elements when considering the fact that *Aedes* mosquitoes are day-biters, but keeping in mind that the purpose is eventually to map human hosts in relation to the vector (and possibly of non-human hosts), the list can be kept manageable. For the purpose of this overview of the conceptual framework, we mention residing, recreation, crop growing, and building based activities associated to outdoor surroundings (e.g. schooling). Local contexts may help to identify the most relevant landscape elements: while it is clear that *Aedes* mosquitoes are extremely well adapted to the urban environments, not all built-up areas or human-frequented areas equally support transmission, depending on how well they support human-vector contact. This has been illustrated for example across the border between Mexico and the United States of America where, despite similar climatic conditions, dengue prevalence differs greatly. This relates to human behavior and living conditions (Reiter et al., 2003). In a study of dengue transmission potential on the island of Oahu (Hawaii), residential areas and outdoor recreation were selected to map areas of greatest exposure to mosquito bites (Vanwambeke et al., 2011). If cultivated areas provide mosquito oviposition sites, they may need to be considered here in relation to the human activity of crop growing.

This broad overview of the RBHC for *Aedes*-borne flaviviruses clearly shows that this framework can only be of use if including the human environment. Indeed, these transmission systems are now nearly exclusively relying on human populations, and the vectors are highly adapted to the urban or built-up environment.

#### *Discussion: moving forward with a RBHC for Aedes-borne flaviviruses in an anthropized world*

The RBHC framework offers an integrated perspective of human-environment interactions in the context of zoonotic and vector-borne diseases. It allows identifying precisely the habitat of a pathogen in relation to the habitat of the species necessary to its transmission cycle. Furthermore, it includes aspects of movement capacity. This may appear of limited interest for the fully urbanized transmission of dengue by *Ae. aegypti*. However, in the case of emerging viruses such as Zika virus, or in areas where the more rural *Ae. albopictus* is prevalent, the movement capacity of vectors and non-human hosts may be more important to consider. Also, the depth of the association between the functional resources of this virus (vectors and hosts) is made striking by the model, as humans appear both as the host, but also as the (unwilling) providers of many of the vector's resources. There could hardly be a more glaring illustration of the importance for health of the issue of human-environment interactions.

Regardless, most other conceptual frameworks that focus on human-environment interactions to understand vector-borne disease transmission, such as One Health (Hartemink et al., 2015, Zinsstag et al., 2011) or Ecohealth (Wilcox et al., 2004), do not offer such a structured approach to pathogen habitat and interactions between the species involved. Only the RBHC framework allows to strictly identify all environmental resources needed for the system to function, allowing thus to formalize the search for the best environmental proxies to the transmission systems. As such, it will be an important complement to broad concepts such as One Health and Ecohealth, and has great potential to contribute to bridging mechanistic and statistical modeling approach (Hartemink et al., 2015).

In this paper we have focused on the landscape scale. Clearly, the landscape scale is the main entry point for understanding the contacts between vectors and hosts in a way that opens up possibilities for control measures. It is the scale at which relevant human activities take place and where land management decisions, including those that can affect disease risk are taken. Other, broader scales of study can however also be approached usefully by the RBHC, and offer for example insight into apparent differences in habitat between environmentally different regions. This has been found for the grayling butterfly (*Hipparchia semele*), which occupies structurally different habitats in different regions in Europe (heathland or forest). The habitats are however similar when considering their correspondence to a functional requirement (Van Dyck, 2012).

One major attraction of the RBHC in the context of *Aedes*-borne flaviviruses may be their usefulness in identifying knowledge gaps and structuring formal question on the ecology of the organism under study. Considering the current situation with Zika virus, and reflecting ongoing preoccupation, several such questions can be highlighted. The risk of introduction in areas that are currently virus-free is a major cause of concern, in particular in relation to international travel, a concern that was raised particularly in the context of the Olympics held in Brazil. Current models deal with this question relatively poorly: empirical statistical models require data to be computed but we are here interested in scenarios never encountered before; and mechanistic models deal poorly with environmental factors in a spatially-explicit context (Hartemink et al., 2015). If confirmed, the presence of the virus in non-human primates in contexts where humans, non-human primates, and mosquitoes interact closely may interfere with control efforts. The functional ecology considered in the RBHC would be useful for this question.

When considering humans, it may appear challenging to identify and map the relevant functions to consider. Indeed, as we are here considering day-biting mosquitoes that live in close association with human populations, it may appear irrelevant and unfeasible to distinguish between diverse human activities. However, not all activities equally expose people: desk work in an air-conditioned office would relate to a very low degree of exposure, and a Central Business District could therefore be excluded in a map of risk. On the other hand, areas where people gather for outdoor social and sport activities are not necessarily found in built-up areas but may provide mosquito habitat as well as intense exposure (Vanwambeke et al., 2011). As suggested above, thanks to the focus on functional aspects of habitats, the RBHC may help to compare existing empirical studies that do not appear coherent or identify differences related to plasticity of the organisms involved.

## Conclusion

Due to the persisting importance of zoonotic and vector-borne diseases in today's world, a thorough understanding of the effect of human-environment interactions on pathogen transmission is



indispensable. The RBHC offers a robust approach to formalizing existing knowledge, structure research questions and data collection, and bridge modeling approaches. By expanding it to humans, we make it useful beyond ecology and for public health. We believe it can be a very useful support to existing, more general conceptual frameworks of environment and health.

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## Figure legend

Figure 1: A resource-based habitat concept adapted to *Aedes*-borne viruses