# Taking a bite out of nutrition and arbovirus infection

James Weger-Lucarelli, Heidi Auerswald, Marco Vignuzzi, Philippe Dussart, Erik A. Karlsson

PLOS | NEGLECTED TROPICAL DISEASES

REVIEW

# Taking a bite out of nutrition and arbovirus infection

**James Weger-Lucarelli[1☯], Heidi Auerswald[2☯], Marco Vignuzzi[1], Phillipe Dussart[2], Erik A. Karlsson[2]***

**1** Viral Populations and Pathogenesis Unit, Institut Pasteur, Centre National de la Recherche Scientifique, Paris, France, **2** Virology Unit, Institut Pasteur du Cambodge, Institut Pasteur International Network, Phnom Penh, Cambodia

☯ These authors contributed equally to this work.
* ekarlsson@pasteur-kh.org

## Abstract

Nutrition is a key factor in host–pathogen defense. Malnutrition can increase both host susceptibility and severity of infection through a number of pathways, and infection itself can promote nutritional deterioration and further susceptibility. Nutritional status can also strongly influence response to vaccination or therapeutic pharmaceuticals. Arthropod-borne viruses (arboviruses) have a long history of infecting humans, resulting in regular pandemics as well as an increasing frequency of autochthonous transmission. Interestingly, aside from host-related factors, nutrition could also play a role in the competence of vectors required for transmission of these viruses. Nutritional status of the host and vector could even influence viral evolution itself. Therefore, it is vital to understand the role of nutrition in the arbovirus lifecycle. This Review will focus on nutritional factors that could influence susceptibility and severity of infection in the host, response to prophylactic and therapeutic strategies, vector competence, and viral evolution.

## Author summary

As the old adage goes, you are what you eat. Proper nutrition is a cornerstone of health, and malnutrition can seriously impair the function of the immune system, resulting in increased infections or a more severe disease. Imbalanced or inadequate nutrition can also affect responses to vaccines or drugs that are vital for protection and treatment against viruses. A mosquito is also a product of what it eats. Nutrition during development and adult lifecycle can affect the feeding behavior of mosquitoes, thereby affecting transmission of viral diseases. Arthropod-borne viruses (arboviruses) are a major global health concern, especially in areas impacted by malnutrition. Understanding how nutrition can affect both humans and mosquitoes in the context of these viruses is vital to combating these diseases.

OPEN ACCESS

**Citation:** Weger-Lucarelli J, Auerswald H, Vignuzzi M, Dussart P, Karlsson EA (2018) Taking a bite out of nutrition and arbovirus infection. PLoS Negl Trop Dis 12(3): e0006247. https://doi.org/10.1371/journal.pntd.0006247

**Editor:** William B. Messer, Oregon Health and Science University, UNITED STATES

**Published:** March 29, 2018



**Funding:** Heidi Auerswald is supported by a postdoctoral fellowship from the Calmette and Yersin Programme of the Institut Pasteur Department of International Affairs. Funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The authors have declared that no competing interests exist.

## Nutrition and infectious disease

Defined as any imbalance resulting in a deficiency or excess, malnutrition is the principal source of immunodeficiency worldwide [1]. Globally, as of 2014, it is estimated that 1.9 billion adults (>18 years of age) are overweight or obese by Body Mass Index (BMI)—18.5 kg/m$^2$ to 24.9 kg/m$^2$ = healthy weight, 25.0 kg/m$^2$ to 29.9 kg/m$^2$ = overweight, and ≥30 kg/m$^2$ = obese —while 462 million are underweight. In children (<5 years of age), around 225 million are undernourished, around 42 million are overweight/obese [2, 3], and approximately 45% of deaths are linked to malnutrition, mainly in developing countries [3]. In lower- to middle-income countries, the rate of increase of childhood obesity is more than 30% higher than in developed countries. Greater than 65% of the global population lives in countries where overweight and obesity kill more people than underweight [2]. Undernutrition is also rampant throughout developed nations [4]. Overall, it is estimated that greater than one-third of the global disease burden could be eliminated by correcting malnutrition [5], and feeding children an adequate diet could prevent approximately 2.5 million deaths per year from pneumonia, diarrhea, malaria, and measles combined [6].

Malnutrition increases host susceptibility and severity of infection through several pathways, including weight loss, immune dysfunction, decreased epithelial integrity, and inflammation. In addition, infection itself can impact host nutritional status through infection-associated anorexia, altered metabolic rate, and altered dietary absorption, further complicating susceptibility and severity [1, 7, 8]. Indeed, frequency of exposure to infectious diseases increases the risk of poor nutrition in a vicious malnutrition–infection–malnutrition cycle [9, 10]. Overall, it is apparent that the interactions between nutrition and infectious disease are complex, with interplay between host, pathogen, and diet. This Review will discuss what is currently known (and unknown) about the relationship between nutritional status and arboviruses in both the vector and the human host.

## What is an arbovirus?

Arboviruses are spread to vertebrate hosts by hematophagous arthropod vectors. Transmission occurs via biological transfer, requiring successful replication in vector species as well as adequate viremia in the host before transmission is achievable. As of 1992, 535 virus species belonging to 14 virus families are registered in the International Catalog of Arboviruses [11], and new viruses are being described on a regular basis [12]. Of these species, greater than 100 are known to cause zoonotic diseases, mainly in four virus families: Togaviridae, Flaviviridae, Bunyaviridae, and Reoviridae [11]. While the majority of arboviruses circulate in tropical and subtropical regions, many arboviruses also have been introduced and thrive within temperate regions. Indeed, these viruses, along with their vector species, have spread exponentially in their geographical distributions in accordance with global trade routes and industrialization [13, 14]. This Review targets arboviruses transmitted by mosquitoes that have high public health importance and risk, namely chikungunya virus (CHIKV; Togaviridae), dengue virus (DENV; Flaviviridae), Zika virus (ZIKV; Flaviviridae), yellow fever virus (YFV; Flaviviridae), Japanese encephalitis virus (JEV; Flaviviridae), and West Nile virus (WNV; Flaviviridae). Combined, these viruses account for hundreds of millions of clinical/symptomatic infections globally, resulting in tens of thousands of deaths per year. However, symptoms in humans and animals range from mild to subclinical infection all the way to encephalitic or hemorrhagic, so the total number of cases per year may be underestimated (Table 1). In addition, due to the paucity of data on nutrition and arbovirus infection, other viruses of concern will also be mentioned where literature is available, including La Crosse virus (LACV; Bunyaviridae), Sindbis virus (SINV; Togaviridae), Ross River virus (RRV; Togaviridae), Western equine encephalitis

**Table 1. Vectors, hosts, symptomology and estimated numbers of cases and deaths of selected arboviruses.**

| Virus | Family | Genus | Main vectors | Reservoir host | Characteristic symptoms (in clinical cases) | Cases/year (estimated) | Symptomatic or severe cases/year | Deaths/ year | References |
|---|---|---|---|---|---|---|---|---|---|
| CHIKV | Togaviridae | *Alphavirus* | *Aedes* spp (in epidemic urban cycle: *A. aegypti*) | Primates | Fever, arthralgia, rash | Outbreak estimates only | Unknown | Unknown | [15] |
| DENV | Flaviviridae | *Flavivirus* | In enzootic cycle: arboreal *Aedes* spp. In epidemic urban cycle: *A. aegypti* and *A. albopictus* | Primates | Fever, hemorrhage | 390 million (95% CI 284–528 million) | 96 million (95% CI 67–136 million) | 12,500 to 22,000 | [16, 17] |
| ZIKV | Flaviviridae | *Flavivirus* | *Aedes* spp | Primates | Fever, rash | Outbreak estimates only | Unknown | Unknown | [18] |
| YFV | Flaviviridae | *Flavivirus* | *Aedes* and *Haemogogus* spp. (in urban cycle: *A. aegypti*) | Primates | Hemorrhage, hepatitis | 200,000 | 84,000 to 170,000 severe cases | 29,000 to 60,000 | [19, 20] |
| JEV | Flaviviridae | *Flavivirus* | *Culex* spp (especially *C. tritaeniorhynchus*) | Birds (Swine as secondary amplification host in epizootic cycle) | Fever, encephalitis | 68,000 | 68,000 clinical cases | 13,600 to 20,400 | [21, 22] |
| WNV | Flaviviridae | *Flavivirus* | *Culex* species (especially *C. pipiens*) | Birds | Fever, encephalitis | Outbreak estimates only | 30,000 to 50,000 | 10,000 to 15,000 | [23, 24] |

**Abbreviations:** DENV, dengue virus; CHIKV, chikungunya virus; JEV, Japanese encephalitis virus; WNV, West Nile virus; YFV, yellow fever virus; ZIKV, Zika virus.

https://doi.org/10.1371/journal.pntd.0006247.t001

virus (WEEV; Togaviridae), Rift Valley Fever virus (RVFV; Bunyaviridae), and St. Louis encephalitis virus (SLEV; Flaviviridae).

## Review methodology

To review what is known on nutrition and arbovirus infection, a comprehensive search was conducted of the peer-reviewed literature available on Pubmed using a number of search terms. Combinations of terms for nutrition (nutrition, diet, feeding, obesity, body mass index, vitamin, micromineral) were used in combination with general and specific terms for arboviruses (arbovirus, alphavirus, flavivirus, bunyavirus, dengue, zika, chikungunya) and/or mosquito-associated terms (mosquito, *Culex*, *Aedes*, vector competence) to find papers related to the Review. All papers were included in the study as long as they pertained to nutritional influences on arboviruses.

## How can nutrition affect arbovirus infection, transmission and severity?

The interplay of transmission cycle, host range, and evolution of arboviruses is a complex process. Arboviruses require a natural host as well as a vector for transmission [25]. While arthropod vectors abound, mosquitoes and ticks carry the most known virus species [11, 25, 26]. Further, of the 300 types of mosquitoes known to transmit arboviruses, female mosquitoes of the genera *Aedes* or *Culex* are most frequently associated with transmission [11, 25]. Arboviral diseases are generally associated with a specific vector and natural host species in rural epizootic and enzootic cycles. Humans and other large mammals tend to be accidental dead-end hosts for many of these cycles; however, spillover transmission to humans can lead to urban epidemic cycles where enzootic amplification is no longer required [25]. Since nutrition is

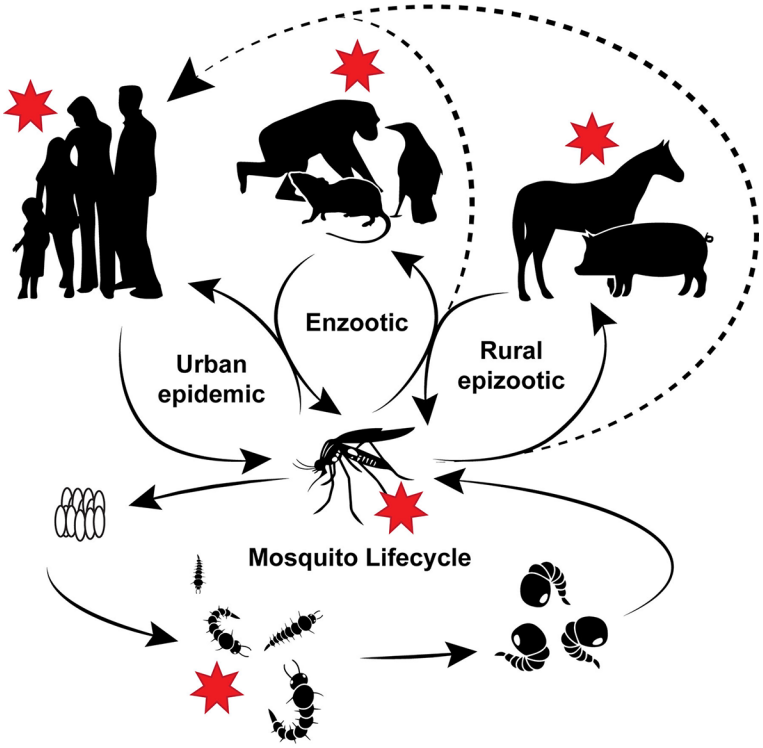


**Fig 1. Influence of nutrition on the arbovirus vector–host cycle.** Growth and development of mosquitoes as well as several pathways (epizootic, enzootic, and urban epidemic) could be impacted by the nutrition of both the host and the vector species. Red stars indicate areas where nutrition could have the most impact on susceptibility, severity of infection, and even vector competence.

https://doi.org/10.1371/journal.pntd.0006247.g001

essential for all organisms, numerous factors could be affected by changing nutritional status in reservoir and secondary amplification hosts as well as enzootic and/or endemic and epidemic vectors (Fig 1).

## Influence of nutrition on reservoir and secondary amplification hosts

Macronutrients and micronutrients are essential for a properly functioning immune system. Numerous nutritional states, such as undernutrition, obesity, and micronutrient deficiencies negatively impact immune function. These immune dysfunctions could then lead to alterations in host susceptibility or infection severity and possibly even increased transmission through changes in vector behavior. Given the global prevalence of malnutrition, particularly in areas hit hardest during arbovirus pandemics (Fig 2), it is essential to understand the connection between arbovirus and host and/or vector nutrition.

### Nutrition and host susceptibility to infection

Few prospective studies have been conducted on nutritional status and arbovirus susceptibility. Therefore, seroprevalence remains the primary means of associating nutrition, infection susceptibility, and arbovirus infection in human hosts (Table 2). Several studies show a strong association between high body weight and obesity and previous arboviral infection. In Madagascar, overweight pregnant women had significantly increased risk for CHIKV seroconversion [27]. On the island of La Réunion, overweight and obese individuals were also at

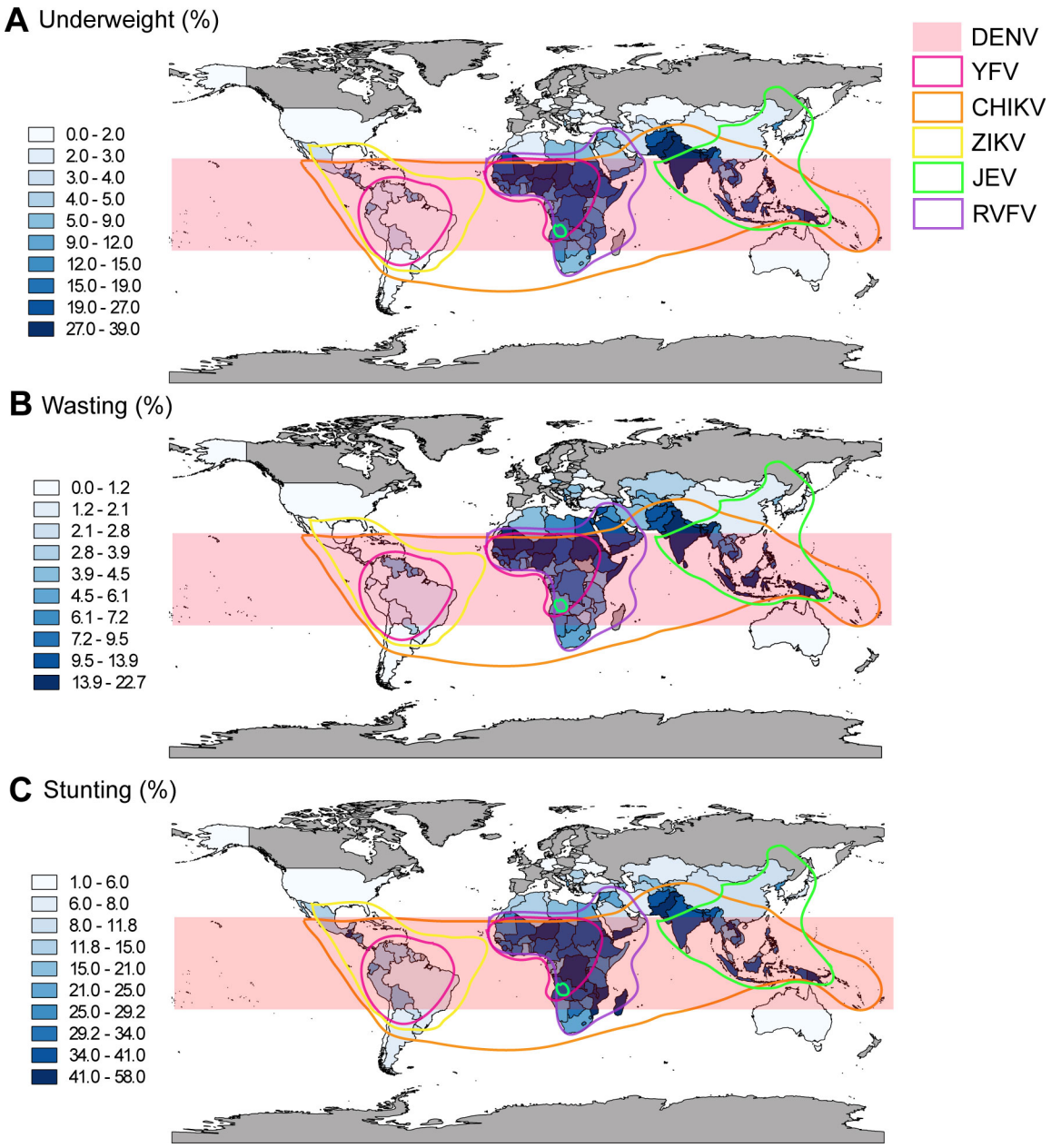


**Fig 2. Correlation of malnutrition with reported distributions of arboviruses.** Prevalence (by percent) of children under the age of 5 that are **(A)** underweight for their age, **(B)** wasted, or **(C)** stunted are shown in blue. Data are the most recent statistics for each country indicated available from the United Nations Children's Fund (available at http://data.unicef.org) and were mapped using QGIS 2.18.12. Overlay colors indicate reported distributions of DENV (light red shading), YFV (pink border), CHIKV (orange border), ZIKV (yellow border), JEV (green border), and RVFV (purple border). Distributions are adapted from Weaver et al. 2017 [214]. CHIKV, chikungunya virus; DENV, dengue virus; JEV, Japanese encephalitis virus; RVFV, Rift Valley Fever virus; YFV, yellow fever virus; ZIKV, Zika virus.

https://doi.org/10.1371/journal.pntd.0006247.g002

increased risk during the 2006 outbreak [28, 29]. Obesity and increased body weight has also been associated with seropositivity for SINV in Sweden [30], DENV in Thailand [31], arboviruses of the genus *Phlebovirus* (family Bunyaviridae), and Toscana virus (TOSV; family Togaviridae) [32]. Overall, further prospective studies in arbovirus-endemic areas are crucial to define the relationship between infection susceptibility and nutritional status.

**Table 2. Seroprevalence studies associating nutrition with infection susceptibility and arbovirus infection in humans.**

| Virus | Country | Age Range (years) | Study Design | Diagnostic Methods | Parameters of Malnutrition | *P*-value or odds ratio (OR) | References |
|---|---|---|---|---|---|---|---|
| CHIKV | Madagascar | 12–50 | Cross-sectional | IFA | Weight >70kg | OR: 9.75, $p = 0.001$. | [27] |
| CHIKV | La Réunion (France) | n/a | Case-control | ELISA | BMI >25 kg/m$^2$ | $p < 0.0001$ | [29] |
| CHIKV | La Réunion (France) | Mean maternal age 28.6–29.1 | Outbreak investigation | Unspecified serology RT-PCR | BMI >30 kg/m$^2$ | BMI = overweight, OR: 1.3. BMI = obese, OR: 1.6. | [28] |
| SINV | Sweden | 25–74 | Cross-sectional survey | EIA | BMI, waist circumference (cm) and diastolic blood pressure (mmHg) | BMI 26.8 versus 27.6, $p = 0.2$. Waist circumference 89.8 versus 93, $p = 0.1$. Diastolic blood pressure 79 versus 82, $p = 0.037$. | [30] |
| TOSV | Italy | 4–75+ | Cross-sectional | EIA | BMI >29.9 kg/m$^2$ | BMI = 25–29.9, OR 1.94. BMI >29.9, OR 2.73 | [32] |
| DENV | Thailand | Mean age 5.8–9.7 | Retrospective Cohort | ELISA and/or HI RT-PCR Virus isolation | Percent ideal body weight (IBW). Obesity defined as >110% IBW and malnutrition <75% IBW. | Malnourished: OR 0.48, $p = 0.000$. Lower chance of contracting dengue fever. Obese: OR 1.96, $p = 0.000$. Higher chance of contracting dengue fever. | [31] |

**Abbreviations:** CHIKV, chikungunya virus; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HI, hemagglutination inhibition assay; IFA, immunoflouresence assay; n/a, not available; RT-PCR, real-time reverse transcriptase polymerase chain reaction; SINV, Sindbis virus; TOSV, Toscana virus.

https://doi.org/10.1371/journal.pntd.0006247.t002

In addition to body weight, the role of micronutrients on arbovirus infection susceptibility is understudied. Vitamins and minerals play a crucial role in immune function and are therefore essential to a proper antiviral defense. Vitamin D can reduce DENV infection and alter proinflammatory cytokine production in vitro [33, 34], and associations between vitamin D receptor gene polymorphisms and risk for DENV infection have been observed in host genetic studies [35]. Vitamin A levels (retinol and β-carotene) have been found to be decreased in DENV patients compared to healthy controls [36]. Zinc has also been shown to be an effective antiviral against many viruses [37]; however, little is known about its role in arbovirus infection aside from antiviral roles in vitro [38, 39]. Overall, further research is needed to scrutinize the relationship between micronutrient status and arbovirus susceptibility.

## Nutrition and arthropod host feeding risk: Can nutrition prevent being bitten?

Aside from host susceptibility, nutrition could also play a vital role in the ability and desire of mosquitoes to bite a given host. In fact, biting rate figures heavily into vectorial capacity, a measurement of the efficiency of vector-borne transmission [40]. Mosquitoes rely on olfaction for locating food sources. Several compounds commonly secreted in human skin, sweat, and breath, such as lactic acid and $CO_2$, are potent mosquito attractants [26–28]. While host genetics plays a major factor in mosquito attractiveness [29], diet has also been suggested as a possible factor for altering individual body odors associated with attraction [41]. Indeed, before the scientific understanding of heritability of attraction, diet was (and possibly still is) the most cited cause of differential susceptibility to mosquito bites. Homeopathic and complementary medicine have suggested several bioactive dietary components that may prevent or encourage mosquito bites to augment traditional preventions and treatments; however, scientific evidence appears to be controversial.

Garlic has been touted as a mosquito repellent since before recorded history, possibly seeding the belief that garlic repels the vampiric behavior of blood consumption. In addition, garlic

supplementation has long been used by dog and horse owners to prevent bites from blood-feeding insects. Scientifically, protection is suggested to be linked with the potent antimicrobial compound allicin [42]. While previous studies suggest some beneficial effect of garlic consumption, a more recent randomized, double-blind, placebo-controlled crossover study found no difference in bites or feeding behaviors of *A*. *aegypti* [43]. Consumption of vitamin B is also commonly prescribed for prevention of mosquito bites, especially vitamin B-1 (thiamine); however, no studies have shown any reduction in mosquito attraction with vitamin B supplementation [44]. Several other dietary ingredients have been purported to reduce mosquito attacks, such as onions, citrus fruits, lemongrass, chilies, apple cider vinegar, and vanilla. While compounds and/or essential oils found in these foods may prove to be effective mosquito repellants [45], no scientific literature is currently available on consumption of these foods in regards to reduction of mosquito attacks or feeding behavior.

Conversely, certain dietary components and nutritional states may increase host "attractiveness" and thereby increase bites. Similar to pregnant woman and individuals performing high-intensity exercise, obese and overweight individuals have increased $CO_2$ production, increasing risk of mosquito bites [46]. Indeed, increased host body mass has been associated with increased and repeat feeding within groups of varied individuals [47]. Alcohol consumption may also alter susceptibility. Several studies have shown that consumption of alcohol as low as a single bottle of beer can increase host attractiveness to several mosquito species [48, 49]. Consumption of potassium-rich and salty foods increases lactic acid production, thereby increasing attractiveness. High-sugar foodstuffs could also increase attractiveness due to the need for nectars and/or plant sugars in the mosquito diet. These claims are currently scientifically unsubstantiated, and further work is necessary to define the role of host nutrition in attraction or prevention of mosquito bites [50].

## Nutrition and severity of infection in the host

Once the host has been bitten and become infected, infection severity is a significant factor in potential outcome. Compared to susceptibility, more studies have observed a relationship between disease severity and nutrition (Table 3). Obese individuals have an increased risk for inflammatory CHIKV sequelae [51], and diabetic status increases CHIKV severity and complications [52, 53]. Severity of WNV, including mortality, has also been associated with diabetes both during the initial outbreak of WNV in the Americas in 1999 [54] and later studies [55]. Furthermore, diabetic mice infected with WNV have increased mortality and impaired viral clearance as compared to healthy controls [56].

Perhaps most is known about the association between nutritional status and DENV severity. Early observational studies suggested no association between poor nutrition and DENV hemorrhagic disease in Thailand [64]. However, later reports showed that malnourished children experience less severe cases of DENV versus those that are well nourished [65, 66]. Further reports provided evidence for these anecdotes [57, 58], and subsequently, this association has also been observed in children in the Philippines and Vietnam [59, 60]. Conversely, obesity has been associated with increased severity of dengue hemorrhagic fever and unusual disease presentation, such as encephalopathy and fluid overload, in several [31, 61, 62] (but not all [63]) studies. Unfortunately, many of these studies do not use consistent definitions for malnutrition or obesity and therefore can be difficult to compare. A large multinational study with consistent parameters for assessment of nutritional status is necessary to truly settle this debate.

Possible links between micronutrients and arbovirus disease severity have also been examined in several studies. Associations between vitamin D levels (measured by overall vitamin D

**Table 3. Relationships between arboviral disease severity and nutritional factors in humans.**

| Virus | Age Range (years) | Study Design | Diagnostic Methods for Infection | Country | Parameters of Malnutrition | *p*-value or odds ratio (OR) | Conclusions | References |
|---|---|---|---|---|---|---|---|---|
| CHIKV | 10–60+ | Cohort | Confirmation by National Institute of Infectious Disease criteria | India | BMI <18.5 kg/m$^2$ as underweight, 18.5–24.9 as normal, 25.0–29.9 as overweight, and ≥ 30 as obese | Overweight, OR: 1.3. Obese, OR: 2.07 | High BMI is associated with CHIKV sequelae | [51] |
| CHIKV | 20+ | Case-control | Commercial rapid diagnostic testing | Haiti | Diabetes mellitus | Severe arthralgia, $p = 0.0002$. Days before arthralgia improvement, $p < 0.0001$. Days with fever, $p = 0.0002$ | Diabetes associated with increased rate of myalgia, greater severity of arthralgia, and longer duration of fever compared to non-diabetic controls | [52] |
| CHIKV | 16+ | Case-control | Fever and/or polyarthralgia RT-PCR ELISA | La Réunion | Diabetes and ischemic heart disease | Diabetes, OR: 2.8. Ischemic heart disease, OR: 5.57 | Patients hospitalized with CHIKV had higher rates of diabetes and ischemic heart disease compared to non-hospitalized controls | [53] |
| WNV | 5–90 | Outbreak surveillance | RT-PCR ELISA | USA | Diabetes mellitus | Encephalitis with muscle weakness, OR: 1.3. Death, OR: 5.1 | Severe WNV disease associated with diabetes mellitus | [54] |
| WNV | 0.4–95 | Nested case-control | ELISA HI PRNT | USA | Diabetes mellitus | Symptomatic WNV infection, OR: 2.0. Death, OR: 3.5 | Severe WNV disease associated with diabetes mellitus | [55] |
| DENV | 2–15.9 | Case-control | HI | Cuba | Defined as % P – E = A / B x 100. Where A = weight kg/height cm and B = 50th percentile of weight for age/ 50th percentile of height | $p > 0.05$ | Did not find an association between nutritional status and dengue complications | [57] |
| DENV | 0.3–15 | Case-control | HI | Thailand | Nutritional status was determined using height, weight and mid-left arm circumference | No patients with 3rd degree malnutrition had severe dengue (no *p*-value could thus be reported) | Patients with severe malnutrition have reduced rates of severe dengue disease | [58] |
| DENV | 0.5–1.5 | Nested case-control | RT-PCR ELISA | Philippines | weight-for-age z-score as defined by WHO. | DHF versus other symptomatic dengue, $p = 0.03$ | A WHO weight-for-age z score <−2 (i.e., undernutrition) during infancy was associated with low risk for DHF | [59] |
| DENV | <1 | Cohort | ELISA | Vietnam | weight-for-age (WA), height-for-age (HA), weight-for-height (WH) z-score as defined by WHO | Developing DHF with undernutrition by WA or HA, $p = 0.03$ and $p < 0.001$, respectively) (negative association). Infants with undernutrition by WH developing DHF, $p < 0.001$ (positive association) | Infants with malnutrition as defined by WA or HA had reduced risk for developing DHF/DSS. Infants with malnutrition defined by WH had increased risk for DHF | [60] |
| DENV | Mean age 5.8–9.7 | Retrospective cohort | ELISA and/or HI RT-PCR Virus isolation | Thailand | Percent ideal body weight (IBW). Obesity defined as >110% IBW and malnutrition <75% IBW | Malnourished versus control, risk of DSS, $p = 0.004$. Obese versus control, risk of DF/DHF, $p < 0.001$ | In patients with DHF, under or overnutrition was associated with severe disease or unusual clinical presentations. Undernutrition was associated with decreased risk of dengue infection | [31] |

(*Continued*)

**Table 3.** (Continued)

| Virus | Age Range (years) | Study Design | Diagnostic Methods for Infection | Country | Parameters of Malnutrition | *p*-value or odds ratio (OR) | Conclusions | References |
|---|---|---|---|---|---|---|---|---|
| DENV | 0.8–16 | Retrospective cohort | Clinical diagnostic criteria defined by the WHO | Thailand | Body weight as a percentile of the normal range for the age | Not reported | The occurrence of severe DHF is more prominent in patients with body weight greater than 50th percentile for age | [61] |
| DENV | 0–14 | Case-control | Clinical diagnostic criteria defined by the WHO | Thailand | Weight-for-height | Obesity versus Control, risk of DHF, $p = 0.001$, OR 3.00 | Obesity is associated with development of DHF | [62]. |
| DENV | 5–12 | Case-control | Clinical diagnostic criteria defined by the WHO ELISA | El Salvador | weight-for-age (WA), BMI-for-age z-score as defined by WHO | Malnourished versus control, risk of DHF, $p = 0.09$ | No differences were observed related to nutritional status and development of dengue fever or hemorraghic fever as compared to controls | [63] |

**Abbreviations:** CHIKV, chikungunya virus; DENV, dengue virus; DF, dengue fever; DHF, dengue hemorrhagic fever; ELISA, enzyme-linked immunosorbent assay; HA, height-for-age; HI, hemagglutination inhibition test; IBW, ideal body weight; PRNT, plaque reduction neutralization test; RT-PCR, real time polymerase chain reaction; WA, weight-for-age; WH, weight-for-height; WNV, West Nile virus

https://doi.org/10.1371/journal.pntd.0006247.t003

status or vitamin D-binding protein) and outcome of dengue fever are mixed [67–69]. Other micronutrients such as zinc [70–72], vitamin A [36], iron [73, 74], copper [73], chromium [75], and vitamin E [76] have also been reported to be associated with development of severe DENV disease. High doses of intravenous vitamin C have been used to treat infection with CHIKV, although more work is needed for confirmation [77]. While more research must be done to improve our understanding of the role of micronutrients and arbovirus disease, there are promising results that suggest ameliorating these nutrient deficiencies or excesses may reduce disease burden and severity.

## Nutrition and prophylactic and therapeutic strategies in the host

Prophylactic and therapeutic strategies are crucial for preventing infection and mitigating disease severity. Nutrition can play a crucial role in these vital strategies. Several arbovirus vaccines are now available or currently in development [78–81] and are critical for many arbovirus-endemic areas of the world, many of which have high rates of one or more nutritional deficiencies (Fig 2). The live-attenuated YFV vaccine, 17D, is by far the most widely administered arbovirus vaccine and has the only vaccine study with nutritional components. Children with kwashiorkor (severe protein deficiency) had a significantly lower seroconversion rate to 17D (12.5%) versus healthy controls (83.3%) [82]. To date, no studies have looked at arboviral vaccines in the obese host; however, several studies have shown obesity can reduce vaccine response or vaccine effectiveness against other pathogens [83–85]. Micronutrients, especially vitamins A and D, are also crucial for vaccination [86–89]. Unfortunately, there is a paucity of information on micronutrients and arbovirus vaccine response. One study showed vitamin A deficiency did not reduce response to YFV 17D vaccine [90]. However, individuals deficient in vitamin A had reduced lymphocyte and cytokine proliferation following vaccination, which could affect long-term vaccine efficacy. Further work is necessary on these crucial nutrients, especially since these viruses are endemic in areas of the world with significant micronutrient deficiencies [3].

In addition to vaccination, the use of antivirals as a therapeutic strategy against arboviruses is critical. During the 1873 YFV epidemic in Memphis, Tennessee, iced champagne was recommended as a curative [91] with negligible effect. Despite research efforts, antiviral treatment for arboviruses has not significantly progressed since that time. While a few antiviral compounds have been tested, few have shown success outside of small-animal laboratory models, and no specific antivirals are currently available for arboviruses [92–94]. Due to the lack of antivirals currently available, several groups have been investigating natural products and medicinal plants as a resource for combating these viruses. These products have a long history as part of traditional medicines and diets [95, 96]. While not necessarily predictive of actual consumption, in vitro studies have revealed potential antiviral effects associated with several common food items. Curcumin, a principal component of the turmeric root, inhibits cell binding of DENV, ZIKV, and CHIKV [97, 98]. Polyphenols such as delphinidin (found in cranberries, grapes, and pomegranates) and epigallocatechin gallate (found in green tea and bananas) have been investigated for their strong antiviral effects against WNV, ZIKV, DENV, and CHIKV in vitro [99, 100]. Papaya leaf and garlic extracts alter the immune response during dengue infection, presumably reducing symptoms during infection without directly affecting viral replication [101, 102]. Additional studies should be performed to assess the antiviral efficacy of these plant-derived compounds. Another issue to consider is the effect of malnutrition on pharmacokinetic processes, drug responses, and toxicity. Diet and nutrition are extremely important to the pharmatoxicological properties of chemicals and malnutrition has been shown to generate therapeutic inadequacies and changes in drug toxicity [103–105].

## Influence of nutrition on arboviral vectors

Aside from the reservoir and secondary hosts, nutrition is also vital for the growth and development of arbovirus vectors and can affect numerous pathways associated with vector susceptibility, viral load and burden, willingness to feed, and even antivector control. For the purposes of this Review, we will focus on nutritional influences on the mosquito genera *Aedes* and *Culex*. The life cycle of hematophagous mosquitoes incorporates four main stages: eggs, larvae (subdivided into four stages called instars), pupae, and adults (Fig 1). Only larvae and adult mosquitoes feed during their development, whereas the other two are inactive stages of metamorphosis in which development is dependent on nutritional reserves [106, 107].

Larvae live in aquatic habitats, feed on organic detritus, bacteria, algae, protozoa, and other microorganisms [108, 109], and seem to feed randomly depending only on abundance. Carbohydrates, minerals (especially calcium), protein (at least the amino acids glycine, leucine, isoleucine, histidine, arginine, lysine, tryptophan, threonine, and methionine), vitamin B complex (thiamin, riboflavin, pyridoxine, nicotinic acid, pantothenic acid, and folic acid), and fat (cholesterol, lecithin, or the fat components of yeast) [110–116] are essential for mosquito development. Appropriate nutrition supports the development from larvae to pupa stage as well as formation of reserves for adult mosquitoes. These reserves consist mainly of lipids and glycogen and support the survival of adults [117–119]. Feeding habits of adult mosquitoes are gender-dependent. Male mosquitoes feed exclusively on sugar and live for around ten days. Female mosquitoes (like some *Aedes* and *Culex* species) consume sugar as well but need blood for the development of their ovaries and eggs (anautogenous). Both sugar and blood are used to produce glycogen and fat reserves in females, which are necessary for their lengthened life span (40–60 days) and egg production [120–122].

Bacteria and microbiome also appear to be vitally important to mosquito development and behavior. All bacteria found in larvae or adult mosquitoes have also been isolated in the water used for oviposition, indicating that larvae ingest the bacteria and transfer them to the adult

stage [123, 124]. Therefore, adults and especially females might take up bacteria from the oviposition sites simply by water contact [125]. Female *C. pipiens* are more attracted to oviposition habitats where *Klebsiella* and *Aeromonas* bacteria are present. These bacteria not only act as food source but are also proposed to be symbionts that can be transferred vertically to the next stages and even the next generation [124–127].

## Nutrition and vector feeding and/or host-seeking behavior

Changes in larval nutritional status can directly affect adult mosquitoes and therefore arbovirus infection in the vector or host. Insufficient diet or starvation during larval development leads to smaller, often weaker adult mosquitoes with fewer reserves and a shorter life span, thereby decreasing chances of transmission and/or infection [128–131]. Restricted larval diet can affect the sex ratio (more males versus females) of *C. molestus*, resulting in fewer mosquitoes searching for a blood meal [132]. Larval nutrition also has a potential effect on adult host-seeking behavior. *A. aegypti* females originating from nutrition-deprived larvae are smaller and show less host-seeking behavior [131]. Interestingly, smaller *Aedes* females also probe more often and take multiple blood meals during one gonotrophic cycle (life cycle of feeding and laying of eggs) [118, 133–136]. This increased contact could enhance the potential of single-host transmission by smaller females despite seeking a host less frequently. On the other hand, larger females have increased host-seeking behavior to cover higher energy requirements [137, 138], increased survival, and more reserves [139], resulting in extended flights [134, 140] and thereby increasing the possibility for transmission to multiple hosts.

Adult nutrition can also impact potential transmission. Feeding on sugar (carbohydrates) prolongs the life span of mosquitoes [119, 141–143]. Indeed, a nutrient-rich adult diet can compensate for life-shortening effects of nutrient deprivation during larval stages in *Aedes* [144–146] and *Culex* [147] species. Sugar deprivation leads to starvation and death [141, 143, 148–152]. Sugar-seeking behavior can also affect propensity of the vector to seek a blood meal. Generally, sugar feeding inhibits the search for a vertebrate host [120, 145, 153–155]. *C. restuans* females feed on nectar when they are unfed (not blood-fed) and when they are carrying eggs (gravid), whereas *A. vexans* females take nectar only while unfed (not blood-fed and/or not gravid). However, both species rarely feed on sugar while digesting a blood meal [156]. Interestingly, females of *C. nigripalpus* show enhanced host-seeking behavior following sucrose feeding, while starved females preferentially feed on honey [157]. For *A. aegypti* females, field observations show infrequent consumption of sugar [158]; however, regular sugar intake is observed under laboratory conditions leading to higher fecundity [121]. In carbohydrate-deprived *A. aegypti*, gravid females attempt to obtain blood meals more often [159].

In contrast to sugar consumption, protein components of blood, specifically amino acids, are necessary for development of the ovarian follicles and oviposition [109]. As such, the host species greatly influences egg number and, subsequently, number of mosquitoes able to transmit arboviruses. *C. quinquefasciatus* females show a higher fertility and fecundity when fed with chicken blood compared to bovine [160]. *A. aegypti* females preferentially feed on humans but will produce more eggs if they feed from other animals, possibly due to the low isoleucine content in human blood [161, 162]. Indeed, *A. aegypti* have adapted to feeding on protein-rich, isoleucine-poor human blood by taking additional blood meals [118, 133, 138, 163–166]. The importance of amino acids for initiation of egg development has been demonstrated by several feeding experiments utilizing artificial diets. *A. aegypti* fed a meal containing only 12 amino acids, including isoleucine, were able to produce eggs [167]. Similarly, feeding of isoleucine-rich globulins versus isoleucine-poor human hemoglobin induced the development of the ovaries and eggs [168, 169]. Interestingly, arbovirus infection itself can also alter

feeding behavior of mosquitoes under laboratory conditions. *A. aegypti* females infected with DENV feed longer [170] and LACV infected *A. triseriatus* females probed more but took less amount of blood than uninfected mosquitoes [171].

## Nutrition and vector competence

Nutrition could also affect vector competence itself (Table 4). For the purposes of this Review, vector competence describes the ability of the vector to become infected with an arbovirus and to show potential to transmit the virus to a host. Overall, existing data on nutritional impacts on vector competence are limited and extremely controversial. Several studies have found that smaller adult females raised from nutrient-deprived larvae showed an increased vector competence. The most extensive studies have been performed using *A. triseriatus* and LACV. Smaller females originating from nutrient-deprived larvae had significantly higher viral titers and increased oral transmission versus normal-sized (control) or large (overfed) mosquitoes [172, 173], possibly through higher dissemination rates within the mosquito itself [174]. Inverse correlation between mosquito size and vector competence has been further confirmed with LACV in field-caught *A. triseriatus*, DENV and SINV in *A. albopictus*, and DENV and RRV in *A. aegypti* [175–178]. Similar results are observed with *Culex* mosquitoes. *C. tritaeniorhynchus* reared with a low nutrient diet as larvae had higher JEV titers [179], and smaller females are slightly more susceptible to WNV infection [180].

Other studies have shown opposite or no effect of mosquito size on vector competence. Larger mosquitoes have been shown to be more susceptible to arbovirus infection, particularly

**Table 4. Studies observing the effect of nutrition on vector competence.**

| Effect of smaller size | Putative cause of decreased size | Mosquito Species | Virus | Findings in smaller females | References |
|---|---|---|---|---|---|
| Increased vector competence | Decreased food quantity during larval development | *A. triseriatus* | LACV | Increased oral transmission rates and higher dissemination rates | [173, 174] |
| | Decreased food quantity during larval development | *A. albopictus* | DENV | Increased susceptibility | [181] |
| | Decreased food quantity during larval development | *A. aegypti* | RRV | Larger blood meals (including higher amount of virus uptake) relative to body size | [176] |
| | Lower quality food | *C. tritaeniorhynchus* | JEV | Increased dissemination rates | [179] |
| | Decreased food quantity during larval development and increased larvae density | *C. tritaeniorhynchus* | WNV | Higher infection rates | [180] |
| | Decreased food quantity (and other factors) during larval development | *A. triseriatus* (field-caught) | LACV | Increased dissemination and transmission | [175] |
| No effect on vector competence | Decreased food quantity | *A. vigilax* | RRV | No difference | [182] |
| | Decreased food quantity | *C. tarsalis* | WNV | No difference | [183] |
| | Decreased food quantity | *C. annulisostris* | Murray Valley encephalitis virus | No difference | [184] |
| | Altered salt content in natural habitat | *C. tarsalis* | WEEV, SLEV | No difference | [185] |
| Reduced vector competence | Decreased food quantity and increased density during larval development | *A. aegypti* | DENV | Lower infection rates | [186] |
| | Decreased food quantity during larval development | *A. aegypti* | RRV | Lower infection rates | [176] |

**Abbreviations:** DENV, dengue virus; LACV, La Crosse virus; JEV, Japanese encephalitis virus; RRV, Ross River virus; SLEV, St. Louis encephalitis virus; WEEV, Western equine encephalitis virus; WNV, West Nile virus.

https://doi.org/10.1371/journal.pntd.0006247.t004

*A. aegypti* and DENV [186] and *A. albopictus* and CHIKV [187], possibly due to increased viral receptors in the gut [176]. Some studies have shown no correlation between mosquito size and vector competence [185]. Overall, these studies do suggest that nutrition during larval stages can affect vector competence of the adult mosquito; however, further work is necessary to elucidate the exact mechanism associated with these changes.

Aside from mosquito size, mosquito microbiome may also play an important role in vector competence. Elimination of endogenous bacteria in *A. aegypti* mosquitoes increases susceptibility to DENV [188], and probiotic transfer of *Proteus* bacteria into the midgut increases resistance. Mechanistically, microbiomes may protect mosquitoes from certain arbovirus infections by production of secondary antiviral metabolites [189]. In contrast, microbiota can also decrease the expression of immune genes and therefore increase the susceptibility [188].

### Nutrition as a means of vector control

Prevention of host infection is highly dependent on effective vector control. Most strategies aim to kill larvae directly, interfering with development or sterilizing the adults. Most commonly, these efforts are achieved with chemical growth regulators [190]. However, these hormone analogs can also affect benevolent insect species, and resistance is already found worldwide [191, 192]. Therefore, there is an urgent need for novel vector control strategies, such as nutritional components. As stated above, the mosquito microbiome is necessary for reproduction and can influence vector competence. The most popular vector control strategy utilizing bacteria is based on endosymbiotic *Wolbachia*. *Wolbachia* are not ingested directly but are maternally transmitted from infected females to their offspring. Introduction of new *Wolbachia* species into field populations reduces the mosquito reproduction as well as infection susceptibility and transmission potential for several arboviruses such as DENV [193–196], CHIKV [193–197], and YFV [197]. The mechanism is not completely understood; however, direct competition between the endosymbiotic bacteria and arbovirus is postulated [195, 196, 198]. Specific *Wolbachia* strains can also decrease mosquito lifespan, reducing the likelihood of arbovirus transmission [199].

Another strategy for vector control is to introduce larvicidal components that are ingested by larvae in situ. Several bacteria produce larvicidal proteins that have been successfully applied for vector control [200, 201], and several plant extracts and leaf litter also demonstrate larvicidal activity [202, 203]. Algae ingested by mosquito larvae can also have larvicidal effects [204], mainly through production of toxins [205] or starvation [126, 206, 207]. More work is necessary to identify other dietary components or interventions that are more effective in pan-species mosquito population reduction.

## Influence of nutrition on arboviruses themselves

RNA viruses, such as arboviruses, intrinsically exist as heterogeneous, highly mutable populations that can quickly take advantage of environmental conditions [208]. It is by this mechanism that arboviruses can quickly adapt to new vectors and hosts [209]. Since nutritional status has such a profound influence on the host and/or vector, it can also act as a driving force in the emergence of new viral variants [210]. Nutritional status has been found to directly influence virulence in several RNA viruses, including coxsackievirus [211] and influenza virus [212, 213]. Overall, changes in nutritional status can result in point mutations, increasing virulence and/or adaptation when reintroduced to a new host. These mutations could result from reduced viral population bottlenecks due to compromised immune responses or novel viral mutations from increased exposure to inflammation and reactive oxygen species [210]. While no studies have directly observed the influence of nutrition on arbovirus mutation and

population dynamics, future work will focus on these factors in different nutritional states in both host and vector species.

## Conclusions and future perspectives

The number of arbovirus infections increases steadily on a yearly basis and the exact causes for the increased frequency of arboviral outbreaks are not fully understood. Combining the global prevalence of malnutrition with continual arbovirus pandemics, increasing frequency of autochthonous transmission, and the paucity of adequate vaccination and antiviral strategies, it is essential to understand the connection between arbovirus susceptibility and severity and host and vector nutrition. Nutritional status is known to play a major role in immune status and in the development, physiology, and behavior of several mosquito species. Taken together, modulation of nutritional status or amelioration of malnutrition seems to be a targetable method of interrupting transmission as well as reducing susceptibility and disease severity.

### Key learning points

- Nutrition is an understudied aspect of arbovirus infections.
- Compromised nutritional status (malnutrition) is rampant in areas with emerging or endemic arbovirus infections.
- Nutrition is a critical component of host susceptibility to infection and disease severity, with malnutrition leading to increased chance of becoming infected or having more severe infection outcomes.
- Malnutrition can severely impact ability to respond to prophylactic and therapeutic strategies against arbovirus infection.
- Nutritional status of vector species, especially during larval development, can significantly impact host-seeking behaviors and vector competence, resulting in changes in virus transmission.

### Top five papers

1. Kalayanarooj S, Nimmannitya S. Is dengue severity related to nutritional status? Southeast Asian Southeast Asian Journal of Tropical Medicine and Public Health. 2005;36(2):378–84.
2. Ahmed S, Finkelstein JL, Stewart AM, Kenneth J, Polhemus ME, Endy TP, et al. Micronutrients and Dengue. American Journal of Tropical Medicne and Hygeine. 2014;91(5):1049–56.
3. Klowden MJ, Blackmer JL, Chambers GM. Effects of larval nutrition on the host-seeking behavior of adult Aedes aegypti mosquitoes. Journal of the American Mosquito Control Association. 1988;4(1):73–5.
4. Grimstad PR, Walker ED. Aedes triseriatus (Diptera: Culicidae) and La Crosse virus. IV. Nutritional deprivation of larvae affects the adult barriers to infection and transmission. Journal of Medical Entomology. 1991;28(3):378–86.

5. Lefèvre T, Gouagna L-C, Dabiré KR, Elguero E, Fontenille D, Renaud F, et al. Beer Consumption Increases Human Attractiveness to Malaria Mosquitoes. PLoS ONE. 2010;5(3):e9546. doi: 10.1371/journal.pone.0009546

## Acknowledgments

The authors would like to thank Sébastien Boyer, Didier Fontenille, and Annika Suttie for discussions regarding the manuscript.

## References

1. Katona P, Katona-Apte J. The Interaction between Nutrition and Infection. Clinical Infectious Diseases. 2008; 46(10):1582–8. https://doi.org/10.1086/587658 PMID: 18419494
2. World Health Organization. Fact Sheet 311: Obesity 2016 [cited 2017 July 31]. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/.
3. World Health Organization. Fact sheet: Malnutrition 2017 [cited 2017 31 July]. Available from: http://www.who.int/mediacentre/factsheets/malnutrition/en/.
4. Chapman IM. Nutritional Disorders in the Elderly. Medical Clinics of North America. 2006; 90(5):887–907. https://doi.org/10.1016/j.mcna.2006.05.010 PMID: 16962848
5. Disease Control Priorities Project. Eliminating Malnutrition Could Reduce Poor Countries' Disease Burden by One-Third. 2007.
6. Caulfield LE, de Onis M, Blössner M, Black RE. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. The American Journal of Clinical Nutrition. 2004; 80(1):193–8. PMID: 15213048
7. Thurnham DI, Northrop-Clewes CA. Effects of infection on nutritional and immune status. In: Hughes DA, Darlington LG, Bendich A, editors. Diet and human immune function. Nutrition and Health. Totowa, NJ: Humana Press; 2004. p. 35–66.
8. Keusch GT. The history of nutrition: malnutrition, infection and immunity. J Nutr. 2003; 133(1):336S–40S. PMID: 12514322.
9. Calder PC, Jackson AA. Undernutrition, infection and immune function. Nutr Res Rev. 2002; 13:3–29.
10. Scrimshaw NS, Taylor CE, Gordon JE. Interactions of nutrition and infecton. Am J Med Sci. 1959; 237:367–403. PMID: 13626979
11. Karabatsos NE. International catalogue of arboviruses, including certain other viruses of vertebrates. 3rd ed. ed. Karabatsos N, editor. San Antonio, Texas:: American Society of Tropical Medicine and Hygiene for The Subcommittee on Information Exchange of the American Committee on Arthropod-borne Viruses; 1985.
12. Junglen S, Drosten C. Virus discovery and recent insights into virus diversity in arthropods. Curr Opin Microbiol. 2013; 16(4):507–13. https://doi.org/10.1016/j.mib.2013.06.005 PMID: 23850098.
13. Liang G, Gao X, Gould EA. Factors responsible for the emergence of arboviruses; strategies, challenges and limitations for their control. Emerg Microbes Infect. 2015; 4:e18. https://doi.org/10.1038/emi.2015.18 PMID: 26038768
14. Gubler DJ. The global emergence/resurgence of arboviral diseases as public health problems. Arch Med Res. 2002; 33(4):330–42. PMID: 12234522.
15. World Health Organization. Fact Sheet 327: Chikungunya 2017 [cited 2017 July 31st]. Available from: http://www.who.int/mediacentre/factsheets/fs327/en/.
16. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013; 496(7446):504–7. https://doi.org/10.1038/nature12060 PubMed PMID: PMC3651993. PMID: 23563266
17. World Health Organization. Fact Sheet 117: Dengue and severe dengue 2017 [cited 2017 July 31]. Available from: http://www.who.int/mediacentre/factsheets/fs117/en/.
18. World Health Organization. Fact Sheet: Zika virus 2016 [cited 2017 July 31st]. Available from: http://www.who.int/mediacentre/factsheets/zika/en/.

19. Barnett ED. Yellow Fever: Epidemiology and Prevention. Clinical Infectious Diseases. 2007; 44 (6):850–6. https://doi.org/10.1086/511869 PMID: 17304460

20. World Health Organization. Fact Sheet 100: Yellow fever 2016 [cited 2017 July 31st]. Available from: http://www.who.int/mediacentre/factsheets/fs100/en/.

21. World Health Organization. Fact Sheet 386: Japanese encephalitis 2015 [cited 2017 July 31st]. Available from: http://www.who.int/mediacentre/factsheets/fs386/en/.

22. Campbell GL, Hills SL, Fischer M, Jacobson JA, Hoke CH, Hombach JM, et al. Estimated global incidence of Japanese encephalitis: a systematic review. Bulletin of the World Health Organization. 2011; 89(10):766–74E. https://doi.org/10.2471/BLT.10.085233 PubMed PMID: PMC3209971. PMID: 22084515

23. World Health Organization. Fact Sheet 354: West Nile virus 2011 [cited 2017 July 31st]. Available from: http://www.who.int/mediacentre/factsheets/fs354/en/.

24. Solomon T. Flavivirus Encephalitis. New England Journal of Medicine. 2004; 351(4):370–8. https://doi.org/10.1056/NEJMra030476 PMID: 15269317.

25. Weaver SC, Barrett AD. Transmission cycles, host range, evolution and emergence of arboviral disease. Nat Rev Microbiol. 2004; 2(10):789–801. https://doi.org/10.1038/nrmicro1006 PMID: 15378043.

26. Adelman ZN, Miller DM, Myles KM. Bed bugs and infectious disease: a case for the arboviruses. PLoS Pathog 2013; 9(8):e1003462. https://doi.org/10.1371/journal.ppat.1003462 PMID: 23966852; PubMed Central PMCID: PMCPMC3744395.

27. Schwarz NG, Girmann M, Randriamampionona N, Bialonski A, Maus D, Krefis AC, et al. Seroprevalence of antibodies against Chikungunya, Dengue, and Rift Valley fever viruses after febrile illness outbreak, Madagascar. Emerg Infect Dis. 2012; 18(11):1780–6. https://doi.org/10.3201/eid1811.111036 PMID: 23092548; PubMed Central PMCID: PMCPMC3559170.

28. Gerardin PP J.; Fianu A.; Favier F. Determinants of chikungunya virus infection in the Reunion Island: Results of the SEROCHIK seroprevalence survey in the population, August-October 2006 Bulletin épidémiologique hebdomadaire. 2008; n°38-39-40:361–3.

29. Fritel X, Rollot O, Gerardin P, Gauzere BA, Bideault J, Lagarde L, et al. Chikungunya virus infection during pregnancy, Reunion, France, 2006. Emerg Infect Dis. 2010; 16(3):418–25. https://doi.org/10.3201/eid1603.091403 PMID: 20202416; PubMed Central PMCID: PMCPMC3322036.

30. Ahlm C, Eliasson M, Vapalahti O, Evander M. Seroprevalence of Sindbis virus and associated risk factors in northern Sweden. Epidemiol Infect. 2014; 142(7):1559–65. https://doi.org/10.1017/S0950268813002239 PMID: 24029159.

31. Kalayanarooj S, Nimmannitya S. Is dengue severity related to nutritional status? Southeast Asian J Trop Med Public Health. 2005; 36(2):378–84. PMID: 15916044.

32. Calamusa G, Valenti RM, Vitale F, Mammina C, Romano N, Goedert JJ, et al. Seroprevalence of and risk factors for Toscana and Sicilian virus infection in a sample population of Sicily (Italy). J Infect. 2012; 64(2):212–7. https://doi.org/10.1016/j.jinf.2011.11.012 PMID: 22120113; PubMed Central PMCID: PMCPMC3630500.

33. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol. 2008; 8(9):685–98. https://doi.org/10.1038/nri2378 PMID: 19172691; PubMed Central PMCID: PMCPMC2906676.

34. Puerta-Guardo H, Medina F, De la Cruz Hernandez SI, Rosales VH, Ludert JE, del Angel RM. The 1alpha,25-dihydroxy-vitamin D3 reduces dengue virus infection in human myelomonocyte (U937) and hepatic (Huh-7) cell lines and cytokine production in the infected monocytes. Antiviral Res. 2012; 94 (1):57–61. https://doi.org/10.1016/j.antiviral.2012.02.006 PMID: 22387385.

35. Alagarasu K, Honap T, Mulay AP, Bachal RV, Shah PS, Cecilia D. Association of vitamin D receptor gene polymorphisms with clinical outcomes of dengue virus infection. Hum Immunol. 2012; 73 (11):1194–9. https://doi.org/10.1016/j.humimm.2012.08.007 PMID: 22917542.

36. Klassen P, Biesalski HK, Mazariegos M, Solomons NW, Furst P. Classic dengue fever affects levels of circulating antioxidants. Nutrition. 2004; 20(6):542–7. https://doi.org/10.1016/j.nut.2004.03.016 PMID: 15165617.

37. Polatnick J, Bachrach HL. Effect of zinc and other chemical agents on foot-and-mouth-disease virus replication. Antimicrobial agents and chemotherapy. 1978; 13(5):731–4. PMID: 208461; PubMed Central PMCID: PMC352324.

38. Jan JT, Chen BH, Ma SH, Liu CI, Tsai HP, Wu HC, et al. Potential dengue virus-triggered apoptotic pathway in human neuroblastoma cells: arachidonic acid, superoxide anion, and NF-kappaB are sequentially involved. Journal of virology. 2000; 74(18):8680–91. PMID: 10954569; PubMed Central PMCID: PMC116379.

39. Shafee N, AbuBakar S. Zinc accelerates dengue virus type 2-induced apoptosis in Vero cells. FEBS letters. 2002; 524(1–3):20–4. PMID: 12135735.

40. Scott TW, Takken W. Feeding strategies of anthropophilic mosquitoes result in increased risk of pathogen transmission. Trends Parasitol. 2012; 28(3):114–21. https://doi.org/10.1016/j.pt.2012.01.001 PMID: 22300806.

41. Havlicek J, Lenochova P. Environmental Effects on Human Body Odour. In: Hurst JL, Beynon RJ, Roberts SC, Wyatt TD, editors. Chemical Signals in Vertebrates 11. New York, NY: Springer New York; 2008. p. 199–210.

42. Kyung KH. Antimicrobial properties of allium species. Current Opinion in Biotechnology. 2012; 23 (2):142–7. https://doi.org/10.1016/j.copbio.2011.08.004 PMID: 21903379

43. Rajan TV, Hein M, Porte P, Wikel S. A double-blinded, placebo-controlled trial of garlic as a mosquito repellant: a preliminary study. Medical and Veterinary Entomology. 2005; 19(1):84–9. https://doi.org/10.1111/j.0269-283X.2005.00544.x PMID: 15752181

44. Ives AR, Paskewitz SM. Testing vitamin B as a home remedy against mosquitoes. Journal of the American Mosquito Control Association. 2005; 21(2):213–7. https://doi.org/10.2987/8756-971X(2005)21[213:TVBAAH]2.0.CO;2 PMID: 16033124

45. Nerio LS, Olivero-Verbel J, Stashenko E. Repellent activity of essential oils: A review. Bioresource Technology. 2010; 101(1):372–8. https://doi.org/10.1016/j.biortech.2009.07.048 PMID: 19729299

46. Sood A, Dixon AE. Effect of obesity on the development and clinical presentation of asthma. In: Dixon AE, Clerisme-Beaty EM, editors. Obesity and Lung Disease; A Guide to Management. New York: Human Press; 2013. p. 119–38.

47. Port GR, Boreham PFL, Bryan JH. The relationship of host size to feeding by mosquitoes of the Anopheles gambiae Giles complex (Diptera: Culicidae). Bulletin of Entomological Research. 2009; 70 (1):133–44. Epub 07/01. https://doi.org/10.1017/S0007485300009834

48. Shirai O, Tsuda T, Kitagawa S, Naitoh K, Seki T, Kamimura K, et al. Alcohol ingestion stimulates mosquito attraction. Journal of the American Mosquito Control Association. 2002; 18(2):91–6. PMID: 12083361.

49. Lefèvre T, Gouagna L-C, Dabiré KR, Elguero E, Fontenille D, Renaud F, et al. Beer Consumption Increases Human Attractiveness to Malaria Mosquitoes. PLoS ONE. 2010; 5(3):e9546. https://doi.org/10.1371/journal.pone.0009546 PMID: 20209056

50. Shirai O, Tsuda T, Kitagawa S, Naitoh K, Seki T, Kamimura K, et al. Alcohol ingestion stimulates mosquito attraction. J Am Mosq Control Assoc. 2002; 18(2):91–6. PMID: 12083361.

51. Padmakumar B, Jayan JB, Menon R, Kottarathara AJ. Clinical profile of chikungunya sequelae, association with obesity and rest during acute phase. Southeast Asian J Trop Med Public Health. 2010; 41 (1):85–91. PMID: 20578486.

52. Jean-Baptiste E, von Oettingen J, Larco P, Raphael F, Larco NC, Cauvin MM, et al. Chikungunya Virus Infection and Diabetes Mellitus: A Double Negative Impact. Am J Trop Med Hyg. 2016; 95 (6):1345–50. https://doi.org/10.4269/ajtmh.16-0320 PMID: 27729569; PubMed Central PMCID: PMCPMC5154448.

53. Borgherini G, Poubeau P, Staikowsky F, Lory M, Le Moullec N, Becquart JP, et al. Outbreak of chikungunya on Reunion Island: early clinical and laboratory features in 157 adult patients. Clin Infect Dis. 2007; 44(11):1401–7. https://doi.org/10.1086/517537 PMID: 17479933.

54. Nash D, Mostashari F, Fine A, Miller J, O'Leary D, Murray K, et al. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med. 2001; 344(24):1807–14. https://doi.org/10.1056/NEJM200106143442401 PMID: 11407341.

55. Murray K, Baraniuk S, Resnick M, Arafat R, Kilborn C, Cain K, et al. Risk factors for encephalitis and death from West Nile virus infection. Epidemiol Infect. 2006; 134(6):1325–32. https://doi.org/10.1017/S0950268806006339 PMID: 16672108; PubMed Central PMCID: PMCPMC2870518.

56. Kumar M, Roe K, Nerurkar PV, Namekar M, Orillo B, Verma S, et al. Impaired virus clearance, compromised immune response and increased mortality in type 2 diabetic mice infected with West Nile virus. PLoS ONE. 2012; 7(8):e44682. https://doi.org/10.1371/journal.pone.0044682 PMID: 22953001; PubMed Central PMCID: PMCPMC3432127.

57. Arguelles JM, Hernandez M, Mazart I. [Nutritional evaluation of children and adolescents with a diagnosis of dengue]. Bol Oficina Sanit Panam. 1987; 103(3):245–51. PMID: 2959297.

58. Thisyakorn U, Nimmannitya S. Nutritional status of children with dengue hemorrhagic fever. Clin Infect Dis. 1993; 16(2):295–7. PMID: 8443312.

59. Libraty DH, Zhang L, Woda M, Giaya K, Kathivu CL, Acosta LP, et al. Low adiposity during early infancy is associated with a low risk for developing dengue hemorrhagic fever: a preliminary model.

PLoS ONE 2014; 9(2):e88944. https://doi.org/10.1371/journal.pone.0088944 PMID: 24533162; PubMed Central PMCID: PMCPMC3923068.

60. Nguyen TH, Nguyen TL, Lei HY, Lin YS, Le BL, Huang KJ, et al. Association between sex, nutritional status, severity of dengue hemorrhagic fever, and immune status in infants with dengue hemorrhagic fever. Am J Trop Med Hyg. 2005; 72(4):370–4. PMID: 15827272.

61. Chuansumrit A, Phimolthares V, Tardtong P, Tapaneya-Olarn C, Tapaneya-Olarn W, Kowsathit P, et al. Transfusion requirements in patients with dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health. 2000; 31(1):10–4. PMID: 11023057.

62. Pichainarong N, Mongkalangoon N, Kalayanarooj S, Chaveepojnkamjorn W. Relationship between body size and severity of dengue hemorrhagic fever among children aged 0–14 years. Southeast Asian J Trop Med Public Health. 2006; 37(2):283–8. PMID: 17124987.

63. Maron GM, Clara AW, Diddle JW, Pleites EB, Miller L, Macdonald G, et al. Association between nutritional status and severity of dengue infection in children in El Salvador. Am J Trop Med Hyg. 2010; 82 (2):324–9. https://doi.org/10.4269/ajtmh.2010.09-0365 PMID: 20134012; PubMed Central PMCID: PMCPMC2813176.

64. Halstead SB. Dengue and hemorrhagic fevers of Southeast Asia. Yale J Biol Med. 1965; 37(6):434–54. PMID: 5837996; PubMed Central PMCID: PMCPMC2604746.

65. Hendrickse RG. Aspects of tropical paediatrics. Trans R Soc Trop Med Hyg. 1976; 70(4):268–73. PMID: 795103.

66. Halstead SB. Dengue haemorrhagic fever—a public health problem and a field for research. Bull World Health Organ. 1980; 58(1):1–21. PMID: 6966540; PubMed Central PMCID: PMCPMC2395896.

67. Alagarasu K, Bachal RV, Bhagat AB, Shah PS, Dayaraj C. Elevated levels of vitamin D and deficiency of mannose binding lectin in dengue hemorrhagic fever. Virol J. 2012; 9:86. https://doi.org/10.1186/1743-422X-9-86 PMID: 22559908; PubMed Central PMCID: PMCPMC3413536.

68. Albuquerque LM, Trugilho MR, Chapeaurouge A, Jurgilas PB, Bozza PT, Bozza FA, et al. Two-dimensional difference gel electrophoresis (DiGE) analysis of plasmas from dengue fever patients. J Proteome Res. 2009; 8(12):5431–41. https://doi.org/10.1021/pr900236f PMID: 19845402.

69. Sanchez-Valdez E, Delgado-Aradillas M, Torres-Martinez JA, Torres-Benitez JM. Clinical response in patients with dengue fever to oral calcium plus vitamin D administration: study of 5 cases. Proc West Pharmacol Soc. 2009; 52:14–7. PMID: 22128411.

70. Yuliana N, Fadil RR, Chairulfatah A. Serum zinc levels and clinical severity of dengue infection in children. 2009. 2009; 49(6):-294. Epub 2009-12-31. https://doi.org/10.14238/pi49.6.2009.309–14

71. Laoprasopwattana K, Tangcheewawatthanakul C, Tunyapanit W, Sangthong R. Is zinc concentration in toxic phase plasma related to dengue severity and level of transaminases? PLoS Negl Trop Dis 2013; 7(6):e2287. https://doi.org/10.1371/journal.pntd.0002287 PMID: 23819001; PubMed Central PMCID: PMCPMC3688526.

72. Widagdo. Blood zinc levels and clinical severity of dengue hemorrhagic fever in children. Southeast Asian J Trop Med Public Health. 2008; 39(4):610–6. PMID: 19058597.

73. Soundravally R, Sherin J, Agieshkumar BP, Daisy MS, Cleetus C, Narayanan P, et al. Serum Levels of Copper and Iron in Dengue Fever. Rev Inst Med Trop Sao Paulo. 2015; 57(4):315–20. https://doi.org/10.1590/S0036-46652015000400007 PMID: 26422155; PubMed Central PMCID: PMCPMC4616916.

74. Chaiyaratana W, Chuansumrit A, Atamasirikul K, Tangnararatchakit K. Serum ferritin levels in children with dengue infection. Southeast Asian J Trop Med Public Health. 2008; 39(5):832–6. PMID: 19058577.

75. Shrivastava R, Srivastava S, Upreti RK, Chaturvedi UC. Effects of dengue virus infection on peripheral blood cells of mice exposed to hexavalent chromium with drinking water. Indian J Med Res. 2005; 122 (2):111–9. PMID: 16177467.

76. Vaish A, Verma S, Agarwal A, Gupta L, Gutch M. Effect of vitamin E on thrombocytopenia in dengue fever. Annals of Tropical Medicine and Public Health. 2012; 5(4):282–5. https://doi.org/10.4103/1755-6783.102004

77. Gonzalez MJ, Miranda-Massari JR, Berdiel MJ, Duconge J, Rodriguez-Lopez JL, Hunninghake R, et al. High Dose Intraveneous Vitamin C and Chikungunya Fever: A Case Report. J Orthomol Med. 2014; 29(4):154–6. PMID: 25705076; PubMed Central PMCID: PMCPMC4335641.

78. Guy B, Saville M, Lang J. Development of Sanofi Pasteur tetravalent dengue vaccine. Hum Vaccin. 2010; 6(9). https://doi.org/10.4161.hv.6.9.12739 PMID: 20861669.

79. Saez-Llorens X, Tricou V, Yu D, Rivera L, Tuboi S, Garbes P, et al. Safety and immunogenicity of one versus two doses of Takeda's tetravalent dengue vaccine in children in Asia and Latin America: interim

results from a phase 2, randomised, placebo-controlled study. Lancet Infect Dis. 2017; 17(6):615–25. https://doi.org/10.1016/S1473-3099(17)30166-4 PMID: 28365225.

80. Kirkpatrick BD, Whitehead SS, Pierce KK, Tibery CM, Grier PL, Hynes NA, et al. The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model. Sci Transl Med. 2016; 8(330):330ra36. https://doi.org/10.1126/scitranslmed.aaf1517 PMID: 27089205.

81. Dowd KA, Ko SY, Morabito KM, Yang ES, Pelc RS, DeMaso CR, et al. Rapid development of a DNA vaccine for Zika virus. Science. 2016; 354(6309):237–40. https://doi.org/10.1126/science.aai9137 PMID: 27708058; PubMed Central PMCID: PMCPMC5304212.

82. Brown RE, Katz M. Failure of antibody production to yellow fever vaccine in children with kwashiorkor. Trop Geogr Med. 1966; 18(2):125–8. PMID: 5962839.

83. Karlsson EA, Beck MA. The burden of obesity on infectious disease. Experimental Biology and Medicine. 2010; 235(12):1412–24. https://doi.org/10.1258/ebm.2010.010227 PMID: 21127339

84. Karlsson EA, Hertz T, Johnson C, Mehle A, Krammer F, Schultz-Cherry S. Obesity Outweighs Protection Conferred by Adjuvanted Influenza Vaccination. mBio. 2016; 7(4). https://doi.org/10.1128/mBio.01144-16 PMID: 27486196

85. Neidich SD, Green WD, Rebeles J, Karlsson EA, Schultz-Cherry S, Noah TL, et al. Increased risk of influenza among vaccinated adults who are obese. Int J Obes. 2017. https://doi.org/10.1038/ijo.2017.131 PMID: 28584297

86. Jun K, Hiroshi K. Vitamins Mediate Immunological Homeostasis and Diseases at the Surface of the Body. Endocrine, Metabolic & Immune Disorders—Drug Targets. 2015; 15(1):25–30. http://dx.doi.org/10.2174/1871530314666141021114651.

87. Ahmed S, Finkelstein JL, Stewart AM, Kenneth J, Polhemus ME, Endy TP, et al. Micronutrients and Dengue. The American Journal of Tropical Medicine and Hygiene. 2014; 91(5):1049–56. https://doi.org/10.4269/ajtmh.14-0142 PubMed PMID: PMC4228873. PMID: 25200269

88. Sadarangani S, Whitaker JA, Poland GA. "Let There Be Light": The Role of Vitamin D in the Immune Response to Vaccines. Expert review of vaccines. 2015; 14(11):1427–40. https://doi.org/10.1586/14760584.2015.1082426 PubMed PMID: PMC4913549. PMID: 26325349

89. Patel S, Vajdy M. Induction of cellular and molecular immunomodulatory pathways by vitamin A and Flavonoids. Expert opinion on biological therapy. 2015; 15(10):1411–28. https://doi.org/10.1517/14712598.2015.1066331 PubMed PMID: PMC4832596. PMID: 26185959

90. Ahmad SM, Haskell MJ, Raqib R, Stephensen CB. Men with low vitamin A stores respond adequately to primary yellow fever and secondary tetanus toxoid vaccination. J Nutr. 2008; 138(11):2276–83. https://doi.org/10.3945/jn.108.092056 PMID: 18936231; PubMed Central PMCID: PMCPMC3151440.

91. Erskine JH. A report on yellow fever as it appeared in Memphis, Tenn., in 1873. Public Health Pap Rep. 1873; 1:385–92. PMID: 19599870

92. Meltzer E. Arboviruses and Viral Hemorrhagic Fevers (VHF). Infectious Disease Clinics of North America. 2012; 26(2):479–96. https://doi.org/10.1016/j.idc.2012.02.003 PMID: 22632650

93. Bray M. Highly pathogenic RNA viral infections: Challenges for antiviral research. Antiviral Research. 2008; 78(1):1–8. https://doi.org/10.1016/j.antiviral.2007.12.007 PMID: 18243346

94. Neyts J, Leyssen P, De Clercq E. Infections with flaviviridae. Verh K Acad Geneeskd Belg. 1999; 61(6):661–97. PMID: 10655776

95. Frederico ÉHFF, Cardoso ALBD, Moreira-Marconi E, de Sá-Caputo DdC, Guimarães CAS, Dionello CdF, et al. ANTI-VIRAL EFFECTS OF MEDICINAL PLANTS IN THE MANAGEMENT OF DENGUE: A SYSTEMATIC REVIEW. African Journal of Traditional, Complementary, and Alternative Medicines. 2017; 14(4 Suppl):33–40. https://doi.org/10.21010/ajtcam.v14i4S.5 PubMed PMID: PMC5514443. PMID: 28740942

96. Oliveira AFCdS, Teixeira RR, Oliveira ASd, Souza APMd, Silva MLd, Paula SOd. Potential Antivirals: Natural Products Targeting Replication Enzymes of Dengue and Chikungunya Viruses. Molecules. 2017; 22(3). https://doi.org/10.3390/molecules22030505 PMID: 28327521

97. Mounce BC, Cesaro T, Carrau L, Vallet T, Vignuzzi M. Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding. Antiviral Res. 2017; 142:148–57. https://doi.org/10.1016/j.antiviral.2017.03.014 PMID: 28343845.

98. Padilla SL, Rodriguez A, Gonzales MM, Gallego GJ, Castano OJ. Inhibitory effects of curcumin on dengue virus type 2-infected cells in vitro. Arch Virol. 2014; 159(3):573–9. https://doi.org/10.1007/s00705-013-1849-6 PMID: 24081825.

99. Weber C, Sliva K, von Rhein C, Kummerer BM, Schnierle BS. The green tea catechin, epigallocatechin gallate inhibits chikungunya virus infection. Antiviral Res. 2015; 113:1–3. https://doi.org/10.1016/j.antiviral.2014.11.001 PMID: 25446334.

100. Vazquez-Calvo A, Jimenez de Oya N, Martin-Acebes MA, Garcia-Moruno E, Saiz JC. Antiviral Properties of the Natural Polyphenols Delphinidin and Epigallocatechin Gallate against the Flaviviruses West Nile Virus, Zika Virus, and Dengue Virus. Front Microbiol. 2017; 8:1314. https://doi.org/10.3389/fmicb.2017.01314 PMID: 28744282; PubMed Central PMCID: PMCPMC5504193.

101. Hall A, Troupin A, Londono-Renteria B, Colpitts TM. Garlic Organosulfur Compounds Reduce Inflammation and Oxidative Stress during Dengue Virus Infection. Viruses. 2017; 9(7). https://doi.org/10.3390/v9070159 PMID: 28644404; PubMed Central PMCID: PMCPMC5537651.

102. Subenthiran S, Choon TC, Cheong KC, Thayan R, Teck MB, Muniandy PK, et al. Carica papaya Leaves Juice Significantly Accelerates the Rate of Increase in Platelet Count among Patients with Dengue Fever and Dengue Haemorrhagic Fever. Evid Based Complement Alternat Med. 2013; 2013:616737. https://doi.org/10.1155/2013/616737 PMID: 23662145; PubMed Central PMCID: PMCPMC3638585.

103. Krishnaswamy K. Drug metabolism and pharmacokinetics in malnourished children. Clin Pharmacokinet. 1989; 17 Suppl 1:68–88. PMID: 2692941.

104. Bartelink IH, Savic RM, Dorsey G, Ruel T, Gingrich D, Scherpbier HJ, et al. The Effect of Malnutrition on the Pharmacokinetics and Virologic Outcomes of Lopinavir, Efavirenz and Nevirapine in Food Insecure HIV-infected Children in Tororo, Uganda. The Pediatric Infectious Disease Journal. 2015; 34(3): e63–e70. https://doi.org/10.1097/INF.0000000000000603 PubMed PMID: 00006454-201503000-00015. PMID: 25742090

105. Sampson MR, Cohen-Wolkowiez M, Benjamin DK, Capparelli EV, Watt KM. Pharmacokinetics of Antimicrobials in Obese Children. GaBi journal. 2013; 2(2):76–81. https://doi.org/10.5639/gabij.2013.0202.025 PubMed PMID: PMC4084753. PMID: 25009734

106. Clements A. The biology of Mosquitoes2012.

107. Briegel H. Physiological bases of mosquito ecology. Journal of vector ecology. 2003; 28(1):1–11. PMID: 12831123

108. Laird M. The natural history of larval mosquito habitats: Academic Press London; 1988.

109. Clements AN. Biology of Mosquitoes: Development Nutrition and Reproduction. 1 ed: Springer Netherlands; 1992.

110. Akov S. A qualitative and quantitative study of the nutritional requirements of Aedes aegypti L. larvae. Journal of Insect Physiology. 1962; 8(3):319–35. https://doi.org/10.1016/0022-1910(62)90035-5

111. Golberg L, De Meillon B. The nutrition of the larva of Aëdes aegypti Linnaeus. 3. Lipid requirements. Biochemical Journal. 1948; 48(3):372–9.

112. Golberg L, De Meillon B. The nutrition of the larva of Aëdes aegypti Linnaeus. 4. Protein and amino-acid requirements. The Biochemical journal. 1948; 43(3):379–87.

113. Golberg L, De Meillon B, Lavoipierre M. The nutrition of the larva of Aedes aegypti L. II. Essential water-soluble factors from yeast. Journal of Experimental Biology. 1945; 21:90–6.

114. Trager W. Nutrition. In: Roeder KD, editor. New York: John Wiley & Sons, Inc.; 1953. p. 350–86.

115. Singh KRP, Brown AWA. Nutritional requirements of Aedes aegypti L. Journal of Insect Physiology. 1957; 1(3):199–220. https://doi.org/10.1016/0022-1910(57)90036-7

116. Buddington AR. The Nutrition of Mosquito Larvae. Journal of Economic Entomology. 1941; 34 (2):275–81. https://doi.org/10.1093/jee/34.2.275

117. Timmermann SE, Briegel H. Larval growth and biosynthesis of reserves in mosquitoes. Journal of Insect Physiology. 1999; 45(5):461–70. https://doi.org/10.1016/S0022-1910(98)00147-4 PMID: 12770329

118. Briegel H. Metabolic relationship between female body size, reserves, and fecundity of Aedes aegypti. Journal of Insect Physiology. 1990; 36(3):165–72. https://doi.org/10.1016/0022-1910(90)90118-Y

119. Briegel H, Knüsel I, Timmermann SE. Aedes aegypti: size, reserves, survival, and flight potential. Journal of vector ecology. 2001; 26(1):21–31. PMID: 11469181

120. Van Handel E. The obese mosquito. The Journal of physiology. 1965; 181(3):478–86. PMID: 5880372

121. Briegel H, Hefti M, DiMarco E. Lipid metabolism during sequential gonotrophic cycles in large and small female Aedes aegypti. Journal of Insect Physiology. 2002; 48(5):547–54. https://doi.org/10.1016/S0022-1910(02)00072-0 PMID: 12770082

122. Van Handel E, Lum PT. Sex as regulator of triglyceride metabolism in the mosquito. Science. 1961; 134(3494):1979–80. PMID: 13924573

123. Smith TW, Walker ED, Kaufman MG. Bacterial density and survey of cultivable heterotrophs in the surface water of a freshwater marsh habitat of Anopheles quadrimaculatus larvae (Diptera: Culicidae). Journal of the American Mosquito Control Association. 1998; 14(1):72–7. PMID: 9599327

124. Osei-Poku J, Mbogo CM, Palmer WJ, Jiggins FM. Deep sequencing reveals extensive variation in the gut microbiota of wild mosquitoes from Kenya. Molecular Ecology. 2012; 21(20):5138–50. https://doi.org/10.1111/j.1365-294X.2012.05759.x PMID: 22988916

125. Coon KL, Vogel KJ, Brown MR, Strand MR. Mosquitoes rely on their gut microbiota for development. Molecular Ecology. 2014; 23(11):2727–39. https://doi.org/10.1111/mec.12771 PMID: 24766707

126. Díaz-Nieto LM, Alessio C, Perotti MA, Berón CM. Culex pipiens Development Is Greatly Influenced by Native Bacteria and Exogenous Yeast. PLoS ONE. 2016; 11(4):e0153133-e. https://doi.org/10.1371/journal.pone.0153133 PMID: 27055276

127. Pidiyar VJ, Jangid K, Patole MS, Shouche YS. Studies on cultured and uncultured microbiota of wild culex quinquefasciatus mosquito midgut based on 16s ribosomal RNA gene analysis. The American journal of tropical medicine and hygiene. 2004; 70(6):597–603. doi: 70/6/597 [pii]. PMID: 15210998

128. Christophers SR. Aëdes aegypti (L.) the Yellow Fever Mosquito: its Life History, Bionomics and Structure: Cambridge University Press; 1960.

129. Wigglesworth VB. The storage of protein, fat, glycogen and uric acid in the fat body and other tissues of mosquito larvae. Journal of Experimental Biology. 1942; 19:56–77.

130. Lea AO. STUDIES ON THE DIETARY AND ENDOCRINE REGULATION OF AUTOGENOUS REPRODUCTION IN AEDES TAENIORHYNCHUS (WIED.). Journal of medical entomology. 1964; 1:40–4. PMID: 14188823

131. Klowden MJ, Blackmer JL, Chambers GM. Effects of larval nutrition on the host-seeking behavior of adult Aedes aegypti mosquitoes. Journal of the American Mosquito Control Association. 1988; 4 (1):73–5. PMID: 3193101

132. Kassim NFA, Webb CE, Russell RC. The importance of males: larval diet and adult sugar feeding influences reproduction in Culex molestus. Journal of the American Mosquito Control Association. 2012; 28(4):312–6. https://doi.org/10.2987/12-6274R.1 PMID: 23393755

133. Scott TW, Amerasinghe PH, Morrison AC, Lorenz LH, Clark GG, Strickman D, et al. Longitudinal studies of Aedes aegypti (Diptera: Culicidae) in Thailand and Puerto Rico: blood feeding frequency. Journal of medical entomology. 2000; 37(1):89–101. PMID: 15218911

134. Nasci RS. The size of emerging and host-seeking Aedes aegypti and the relation of size to blood-feeding success in the field. Journal of the American Mosquito Control Association. 1986; 2(1):61–2. https://doi.org/10.1101/gr.3715005 PMID: 3507471

135. Chambers GM, Klowden MJ. Correlation of nutritional reserves with a critical weight for pupation in larval Aedes aegypti mosquitoes. Journal of the American Mosquito Control Association. 1990; 6 (3):394–9. PMID: 2230767

136. Farjana T, Tuno N. Multiple blood feeding and host-seeking behavior in Aedes aegypti and Aedes albopictus (Diptera: Culicidae). J Med Entomol. 2013; 50(4):838–46. PMID: 23926783.

137. Klowden MJ, Lea AO. Blood Meal Size as a Factor Affecting Continued Host-Seeking by Aedes Aegypti (L.)*. The American Journal of Tropical Medicine and Hygiene. 1978; 27(4):827–31. doi: doi: https://doi.org/10.4269/ajtmh.1978.27.827. PMID: 686250

138. Xue RD, Edman JD, Scott TW. Age and body size effects on blood meal size and multiple blood feeding by Aedes aegypti (Diptera: Culicidae). Journal of medical entomology. 1995; 32(4):471–4. PMID: 7650708

139. Van Handel E, Day JF. Assay of lipids, glycogen and sugars in individual mosquitoes: correlations with wing length in field-collected Aedes vexans. Journal of the American Mosquito Control Association. 1988; 4(4):549–50. PMID: 3225576

140. Tun-Lin W, Burkot TR, Kay BH. Effects of temperature and larval diet on development rates and survival of the dengue vector Aedes aegypti in north Queensland, Australia. Medical and Veterinary Entomology. 2000; 14(1):31–7. https://doi.org/10.1046/j.1365-2915.2000.00207.x PMID: 10759309

141. Briegel H, Kaiser C. Life-Span of Mosquitoes (Culicidae, Diptera) under Laboratory Conditions. Gerontology. 1973; 19(4):240–9. https://doi.org/10.1159/000211976

142. Foster WA. Mosquito Sugar Feeding and Reproductive Energetics. Annual Review of Entomology. 1995; 40(1):443–74. https://doi.org/10.1146/annurev.ento.40.1.443

143. Nayar JK, Sauerman DM. Physiological effects of carbohydrates on survival, metabolism, and flight potential of female Aedes taeniorhynchus. Journal of Insect Physiology. 1971; 17(11):2221–33. https://doi.org/10.1016/0022-1910(71)90180-6 PMID: 5158362

144. Xue R-D, Barnard DR, Muller GC. Effects of body size and nutritional regimen on survival in adult Aedes albopictus (Diptera: Culicidae). Journal of medical entomology. 2010; 47(5):778–82. PMID: 20939370

145. Braks MAH, Juliano SA, Lounibos LP. Superior reproductive success on human blood without sugar is not limited to highly anthropophilic mosquito species. Medical and Veterinary Entomology. 2006; 20 (1):53–9. https://doi.org/10.1111/j.1365-2915.2006.00612.x PMID: 16608490

146. Costanzo KS, Muturi EJ, Lampman RL, Alto BW. The effects of resource type and ratio on competition with Aedes albopictus and Culex pipiens (Diptera:Culicidae). Journal of medical entomology. 2011; 48 (1):29–38. PMID: 21337945

147. Vrzal EM, Allan SA, Hahn DA. Amino acids in nectar enhance longevity of female Culex quinquefasciatus mosquitoes. Journal of Insect Physiology. 2010; 56(11):1659–64. https://doi.org/10.1016/j.jinsphys.2010.06.011 PMID: 20609367

148. de Meillon B, Sebastian A, Khan ZH. Cane-sugar feeding in Culex pipiens fatigans. Bulletin of the World Health Organization. 1967; 36(1):53–65. PMID: 5298676

149. Andersson IH. The effect of sugar meals and body size on fecundity and longevity of female Aedes communis(Diptera: Culicidae). Physiological Entomology. 1992; 17(3):203–7. https://doi.org/10.1111/j.1365-3032.1992.tb01011.x

150. Harada F, Moriya K, Yabe T. Observations on the survival and longevity of Culex and Aedes mosquitoes fed on the flowers of nectar plants (IV). Medical Entomology and Zoology. 1975; 26(4):193–201. https://doi.org/10.7601/mez.26.193

151. Nayar JK, Pierce PA. The effects of diet on survival, insemination and oviposition of Culex nigripalpus Theobald. Mosquito News. 1980; 40(2):210–7.

152. Diniz DFA, de Albuquerque CMR, Oliva LO, de Melo-Santos MAV, Ayres CFJ. Diapause and quiescence: dormancy mechanisms that contribute to the geographical expansion of mosquitoes and their evolutionary success. Parasites & Vectors. 2017; 10(1):310-. https://doi.org/10.1186/s13071-017-2235-0 PMID: 28651558

153. Nayar JK, Sauerman DM. The Effects of Nutrition on Survival and Fecundity in Florida Mosquitoes Part 3. Utilization of blood and sugar for fecundity. Journal of Medical Entomology. 1975; 12(2):220–5. https://doi.org/10.1093/jmedent/12.2.220 PMID: 240030

154. Nayar JK, Van Handel E. The fuel for sustained mosquito flight. Journal of Insect Physiology. 1971; 17 (3):471–81. https://doi.org/10.1016/0022-1910(71)90026-6

155. Canyon DV, Hii JL, Muller R. Effect of diet on biting, oviposition, and survival of Aedes aegypti (Diptera: Culicidae). Journal of medical entomology. 1999; 36(3):301–8. PMID: 10337099

156. Vargo AM, Foster WA. Gonotrophic state and parity of nectar-feeding mosquitoes. 1984. p. 6–10.

157. Hancock RG, Foster WA. Larval and adult nutrition effects on blood/nectar choice of Culex nigripalpus mosquitoes. Medical and Veterinary Entomology. 1997; 11(2):112–22. https://doi.org/10.1111/j.1365-2915.1997.tb00299.x PMID: 9226638

158. Harrington LC, Edman JD, Scott TW. Why do female Aedes aegypti (Diptera: Culicidae) feed preferentially and frequently on human blood? Journal of medical entomology. 2001; 38(3):411–22. https://doi.org/10.1603/0022-2585-38.3.411 PMID: 11372967

159. Klowden MJ. Effects of sugar deprivation on the host-seeking behaviour of gravid Aedes aegypti mosquitoes. Journal of Insect Physiology. 1986; 32(5):479–83. https://doi.org/10.1016/0022-1910(86)90009-0

160. Richards SL, Anderson SL, Yost Sa. Effects of blood meal source on the reproduction of Culex pipiens quinquefasciatus (Diptera: Culicidae). Journal of Vector Ecology. 2012; 37(1):1–7. https://doi.org/10.1111/j.1948-7134.2012.00194.x PMID: 22548531

161. Greenberg J. Some nutritional requirements of adult mosquitoes (Aedes aegypti) for oviposition. Journal of Nutrition. 1951; 43(1):27–35. PMID: 14851026

162. Chang Y-YH, Judson CL. Amino acid composition of human and guinea pig blood proteins, and ovarian proteins of the yellow fever mosquito Aedes aegypti; and their effects on the mosquito egg production. Comparative Biochemistry and Physiology Part A: Physiology. 1979; 62(3):753–5. https://doi.org/10.1016/0300-9629(79)90134-8

163. Scott TW, Chow E, Strickman D, Kittayapong P, Wirtz Ra, Lorenz LH, et al. Blood-Feeding Patterns of Aedes aegypti (Diptera: Culicidae) Collected in a Rural Thai Village. Journal of Medical Entomology. 1993; 30(5):922–7. https://doi.org/10.1093/jmedent/30.5.922 PMID: 8254642

164. Edman J. Fitness advantages in multiple blood-feeding: the Aedes aegypti example. Ecological Aspects for Application of Genetically Modified Mosquitoes. 2003; 2:63–74.

165. McClelland GAH, Conway GR. Frequency of Blood Feeding in the Mosquito Aedes aegypti. Nature. 1971; 232(5311):485–6. https://doi.org/10.1038/232485a0 PMID: 4937213

166. Edman JD, Strickman D, Kittayapong P, Scott TW. Female Aedes aegypti (Diptera: Culicidae) in Thailand rarely feed on sugar. Journal of medical entomology. 1992; 29(6):1035–8. PMID: 1460619

167. Lea AO, Dimond JB, Delong DM. Role of diet in egg development by mosquitoes (Aedes aegypti). Science. 1956; 123(3203):890–1. PMID: 13324108

168. Spielman A. Bionomics of autogenous mosquitoes. Annual review of entomology. 1971; 16:231–48. https://doi.org/10.1146/annurev.en.16.010171.001311 PMID: 4396449

169. Spielman A, Wong J. Dietary factors stimulating oogenesis in Aedes aegypti. The Biological bulletin. 1974; 147(2):433–42. https://doi.org/10.2307/1540460 PMID: 4441563

170. Platt KB, Lerdthusnee K, Linthicum KJ, Myint KSA, Vaughn DW, Innis BL. Impact of Dengue Virus Infection on Feeding Behavior of Aedes aegypti. The American Journal of Tropical Medicine and Hygiene. 1997; 57(2):119–25. https://doi.org/10.4269/ajtmh.1997.57.119 PMID: 9288801

171. Grimstad PR, Ross QE, Craig GB. Aedes triseriatus (Diptera: Culicidae) and La Crosse virus. II. Modification of mosquito feeding behavior by virus infection. Journal of medical entomology. 1980; 17(1):1–7. https://doi.org/10.1038/203023b0 PMID: 7365753

172. McCombs SD. Effects of differential nutrition of larvae on adult fitness of Aedes triseriatus 1980.

173. Grimstad PR, Haramis LD. Aedes Triseriatus (Diptera: Culicidae) and La Crosse Virus III. Enhanced Oral Transmission by Nutrition-Deprived Mosquitoes. Journal of Medical Entomology. 1984; 21 (3):249–56. https://doi.org/10.1093/jmedent/21.3.249 PMID: 6747998

174. Grimstad PR, Walker ED. Aedes triseriatus (Diptera: Culicidae) and La Crosse virus. IV. Nutritional deprivation of larvae affects the adult barriers to infection and transmission. Journal of medical entomology. 1991; 28(3):378–86. PMID: 1875364

175. Paulson SL, Hawley WA. Effect of body size on the vector competence of field and laboratory populations of Aedes triseriatus for La Crosse virus. Journal of the American Mosquito Control Association. 1991; 7(2):170–5. PMID: 1895074

176. Nasci RS, Mitchell CJ. Larval Diet, Adult Size, and Susceptibility of Aedes aegypti (Diptera: Culicidae) to Infection with Ross River Virus. Journal of Medical Entomology. 1994; 31(1):123–6. https://doi.org/10.1093/jmedent/31.1.123 PMID: 8158614

177. Alto BW, Lounibos LP, Mores CN, Reiskind MH. Larval competition alters susceptibility of adult Aedes mosquitoes to dengue infection. Proceedings Biological sciences. 2008; 275(1633):463–71. https://doi.org/10.1098/rspb.2007.1497 PMID: 18077250

178. Alto BW, Reiskind MH, Lounibos LP. Size alters susceptibility of vectors to dengue virus infection and dissemination. The American journal of tropical medicine and hygiene. 2008; 79(5):688–95. doi: 79/5/688 [pii]. PMID: 18981505

179. Takahashi M. The effects of environmental and physiological conditions of Culex tritaeniorhynchus on the pattern of transmission of Japanese encephalitis virus. Journal of medical entomology. 1976; 13 (3):275–84. PMID: 1011230

180. Baqar S, Hayes CG, Ahmed T. The effect of larval rearing conditions and adult age on the susceptibility of Culex tritaeniorhynchus to infection with West Nile virus. Mosquito News. 1980; 40(2):165–71.

181. Zhang S, He G, Xu L, Lin Q, Zhang S, editors. Effects of larval nutrition on susceptibility of Aedes albopictus to dengue 2 virus1993 1993; Brisbane.

182. Jennings CD, Kay BH. Dissemination barriers to Ross River virus in Aedes vigilax and the effects of larval nutrition on their expression. Medical and Veterinary Entomology. 1999; 13(4):431–8. https://doi.org/10.1046/j.1365-2915.1999.00196.x PMID: 10608233

183. Dodson BL, Kramer LD, Rasgon JL. Larval Nutritional Stress Does Not Affect Vector Competence for West Nile Virus (WNV) in Culex tarsalis. Vector-Borne and Zoonotic Diseases. 2011; 11(11):1493–7. https://doi.org/10.1089/vbz.2011.0662 PMID: 21867417

184. Kay BH, Edman JD, Fanning ID, Mottram P. Larval diet and the vector competence of Culex annulirostris (Diptera: Culicidae) for Murray Valley encephalitis virus. Journal of medical entomology. 1989; 26 (5):487–8. PMID: 2552121

185. Reisen WK, Hardy JL, Presser SB. Effects of water quality on the vector competence of Culex tarsalis (Diptera: Culicidae) for western equine encephalomyelitis (Togaviridae) and St. Louis encephalitis (Flaviviridae) viruses. Journal of medical entomology. 1997; 34(6):631–43. PMID: 9439117

186. Sumanochitrapon W, Strickman D, Sithiprasasna R, Kittayapong P, Innis BL. Effect of size and geographic origin of Aedes aegypti on oral infection with dengue-2 virus. The American journal of tropical medicine and hygiene. 1998; 58(3):283–6. PMID: 9546404

187. Westbrook CJ, Reiskind MH, Pesko KN, Greene KE, Lounibos LP. Larval environmental temperature and the susceptibility of Aedes albopictus Skuse (Diptera: Culicidae) to Chikungunya virus. Vector borne and zoonotic diseases. 2010; 10(3):241–7. https://doi.org/10.1089/vbz.2009.0035 PMID: 19725768

188. Xi Z, Ramirez JL, Dimopoulos G. The Aedes aegypti toll pathway controls dengue virus infection. PLoS Pathog 2008; 4(7):e1000098-e. https://doi.org/10.1371/journal.ppat.1000098 PMID: 18604274

189. Joyce JD, Nogueira JR, Bales AA, Pittman KE, Anderson JR. Interactions between La Crosse virus and bacteria isolated from the digestive tract of Aedes albopictus (Diptera: Culicidae). Journal of medical entomology. 2011; 48(2):389–94. https://doi.org/10.1603/ME09268 PMID: 21485378

190. Wilson TG. The molecular site of action of juvenile hormone and juvenile hormone insecticides during metamorphosis: how these compounds kill insects. Journal of insect physiology. 2004; 50(2–3):111–21. https://doi.org/10.1016/j.jinsphys.2003.12.004 PMID: 15019512

191. Baldacchino F, Caputo B, Chandre F, Drago A, della Torre A, Montarsi F, et al. Control methods against invasive Aedes mosquitoes in Europe: a review. Pest Management Science. 2015; 71 (11):1471–85. https://doi.org/10.1002/ps.4044 PMID: 26037532

192. Bellinato DF, Viana-Medeiros PF, Araújo SC, Martins AJ, Lima JBP, Valle D. Resistance Status to the Insecticides Temephos, Deltamethrin, and Diflubenzuron in Brazilian Aedes aegypti Populations. BioMed research international. 2016; 2016:8603263-. https://doi.org/10.1155/2016/8603263 PMID: 27419140

193. Rancès E, Ye YH, Woolfit M, McGraw EA, O'Neill SL. The Relative Importance of Innate Immune Priming in Wolbachia-Mediated Dengue Interference. PLoS Pathog 2012; 8(2):e1002548-e. https://doi.org/10.1371/journal.ppat.1002548 PMID: 22383881

194. Walker T, Moreira LA. Can Wolbachia be used to control malaria? Memórias do Instituto Oswaldo Cruz. 2011; 106 Suppl:212–7. https://doi.org/10.1590/S0074-02762011000900026

195. Pan X, Zhou G, Wu J, Bian G, Lu P, Raikhel AS, et al. Wolbachia induces reactive oxygen species (ROS)-dependent activation of the Toll pathway to control dengue virus in the mosquito Aedes aegypti. Proceedings of the National Academy of Sciences. 2012; 109(1):E23–E31. https://doi.org/10.1073/pnas.1116932108 PMID: 22123956

196. Moreira LA, Iturbe-Ormaetxe I, Jeffery JA, Lu G, Pyke AT, Hedges LM, et al. A Wolbachia symbiont in Aedes aegypti limits infection with dengue, Chikungunya, and Plasmodium. Cell. 2009; 139(7):1268–78. https://doi.org/10.1016/j.cell.2009.11.042 PMID: 20064373

197. van den Hurk AF, Hall-Mendelin S, Pyke AT, Frentiu FD, McElroy K, Day A, et al. Impact of Wolbachia on Infection with Chikungunya and Yellow Fever Viruses in the Mosquito Vector Aedes aegypti. PLoS Negl Trop Dis 2012; 6(11):e1892-e. https://doi.org/10.1371/journal.pntd.0001892 PMID: 23133693

198. Sinkins SP. Wolbachia and arbovirus inhibition in mosquitoes. Future microbiology. 2013; 8 (10):1249–56. https://doi.org/10.2217/fmb.13.95 PMID: 24059916

199. McMeniman CJ, Lane RV, Cass BN, Fong AWC, Sidhu M, Wang YF, et al. Stable Introduction of a Life-Shortening Wolbachia Infection into the Mosquito Aedes aegypti. Science. 2009; 323(5910):141–4. https://doi.org/10.1126/science.1165326 PMID: 19119237

200. Schnepf E, Crickmore N, Van Rie J, Lereclus D, Baum J, Feitelson J, et al. Bacillus thuringiensis and its pesticidal crystal proteins. Microbiology and molecular biology reviews. 1998; 62(3):775–806. doi: 1092–2172. PMID: 9729609

201. Hertlein MB, Mavrotas C, Jousseaume C, Lysandrou M, Thompson GD, Jany W, et al. A Review of Spinosad as a Natural Product for Larval Mosquito Control. Journal of the American Mosquito Control Association. 2010; 26(1):67–87. https://doi.org/10.2987/09-5936.1 PMID: 20402353

202. Shaalan EA-S, Canyon D, Younes MWF, Abdel-Wahab H, Mansour A-H. A review of botanical phytochemicals with mosquitocidal potential. Environment international. 2005; 31(8):1149–66. https://doi.org/10.1016/j.envint.2005.03.003 PMID: 15964629

203. Park I-K, Lee S-G, Shin S-C, Park J-D, Ahn Y-J. Larvicidal activity of isobutylamides identified in Piper nigrum fruits against three mosquito species. Journal of agricultural and food chemistry. 2002; 50 (7):1866–70. https://doi.org/10.1021/jf011457a PMID: 11902925

204. Marten GG. Larvicidal algae. Journal of the American Mosquito Control Association. 2007; 23(2 Suppl):177–83. https://doi.org/10.2987/8756-971X(2007)23[177:LA]2.0.CO;2 PMID: 17855939

205. Purdy WC. Biological Investigation of California Rice Fields and Attendant Waters with reference to Mosquito Breeding. Public Health Bulletin. 1924; 145:61-.

206. Marten GG. Mosquito control by plankton management: the potential of indigestible green algae. The Journal of tropical medicine and hygiene. 1986; 89(5):213–22. PMID: 2879045

207. Howland LJ. The Nutrition of Mosquito Larvae, with special Reference to their Algal Food. Bulletin of Entomological Research. 1930; 21(04):431-. https://doi.org/10.1017/S0007485300024779

208. Domingo E. Mechanisms of viral emergence. Veterinary Research. 2010; 41(6):38. https://doi.org/10.1051/vetres/2010010 PubMed PMID: PMC2831534. PMID: 20167200

209. Stapleford Kenneth A, Coffey Lark L, Lay S, Bordería Antonio V, Duong V, Isakov O, et al. Emergence and Transmission of Arbovirus Evolutionary Intermediates with Epidemic Potential. Cell Host & Microbe. 2014; 15(6):706–16. http://dx.doi.org/10.1016/j.chom.2014.05.008.

**210.** Beck MA, Handy J, Levander OA. Host nutritional status: the neglected virulence factor. Trends in microbiology. 2004; 12(9):417–23. Epub 2004/09/01. https://doi.org/10.1016/j.tim.2004.07.007 PMID: 15337163.

**211.** Beck MA, Shi Q, Morris VC, Levander OA. Rapid genomic evolution of a non-virulent coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. Nat Med. 1995; 1 (5):433–6. PMID: 7585090.

**212.** Nelson HK, Shi Q, Van Dael P, Schiffrin EJ, Blum S, Barclay D, et al. Host nutritional selenium status as a driving force for influenza virus mutations. The FASEB Journal. 2001. https://doi.org/10.1096/fj.01-0115fje

**213.** Beck MA, Nelson HK, Shi Q, Van Dael P, Schiffrin EJ, Blum S, et al. Selenium deficiency increases the pathology of an influenza virus infection. The FASEB Journal. 2001. https://doi.org/10.1096/fj.00-0721fje

**214.** Weaver SC, Charlier C, Vasilakis N, Lecuit M. Zika, Chikungunya, and Other Emerging Vector-Borne Viral Diseases. Annu Rev Med. 2017. https://doi.org/10.1146/annurev-med-050715-105122 PMID: 28846489.