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Mosquitoes as dangerous intermediaries: communicate on bridges between these insects and human health

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Abstract

Mosquitoes are hematophagous carriers for hundreds of pathogenic viruses that are the etiological agents of human diseases. Malaria, Zika fever, chikungunya and dengue fever, etc., are among the diseases that mosquitoes are involved in transmitting. In nature, mosquito-borne viruses maintain a life cycle between mosquitoes and vertebrates. Malaria, transmitted by Anopheles mosquitoes, remains a major cause of morbidity and mortality worldwide, particularly in sub-Saharan Africa. Understanding mosquito ecology is crucial for malaria control efforts. Zika fever, associated with severe neurological complications, has emerged as a global concern, primarily transmitted by Aedes mosquitoes. Urbanization facilitates the proliferation of Aedes populations, exacerbating viral transmission. Chikungunya, spread by Aedes mosquitoes, has expanded beyond endemic regions due to international travel, causing fever, rash, and joint pain. Dengue fever, caused by dengue viruses transmitted by Aedes mosquitoes, witnesses a global resurgence, with climate factors influencing disease transmission dynamics. Effective mosquito control strategies are essential for mitigating the impact of these vector-borne diseases on global health. The aim of this study is to investigate the impact of mosquito-borne diseases on human health and explore strategies for prevention and management.

Keywords: Mosquito, Malaria, Zika, Chikungunya, Dengue, Vector-borne

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Introduction

It is estimated that mosquitoes are responsible for transmitting diseases to approximately 700 million people annually worldwide, primarily in equatorial tropical and subtropical regions.[1] Annually, mosquito-transmitted diseases, including malaria, dengue, West Nile, Zika, and chikungunya fevers, result in the deaths of around 750,000 individuals.[2] Throughout history, mosquito bites or habitats have been linked to human disease, with mosquitoes being formally identified as intermediate hosts of vertebrate parasites as early as 1878. Over the past century, it has been firmly established that mosquitoes are the most significant arthropods impacting human health (Table 1). Their effects include premature mortality and chronic debilitation, which can strain healthcare resources and diminish human productivity, thereby perpetuating economic hardship. Mosquitoes are found in virtually every region of every continent except Antarctica.[3] Vector-borne diseases tend to spread globally due to increased population mobility, migration, travel, and trade, leading to the rapid and widespread dissemination of vectors and the pathogens they carry.[4] Mosquitoes, members of the Culicidae family, are haematophagous vectors that transmit many human viruses in nature. Most mosquito-borne human viruses, belonging to the Flaviviridae, Togaviridae, and Bunyaviridae families, cause severe human diseases such as haemorrhagic fever, biphasic fever, encephalitis, and meningitis. Mosquito-borne viruses cause hundreds of millions of infections annually.[5] Only female mosquitoes bite and feed on blood to aid in egg development and require areas of standing water to lay their eggs. Some mosquitoes are active from dusk to dawn, while others bite during the day. The primary genera responsible for transmitting diseases are Anopheles, Aedes, and Culex.[1] The primary strategies for reducing the public health burden of most mosquito-borne diseases involve vector-based interventions. Before the advent of insecticides, these interventions relied on environmental management, focusing on eliminating mosquito breeding sites and improving housing with screens to prevent mosquito entry through doors and windows. Following World War II, insecticides like DDT and dieldrin were developed for indoor and outdoor use, eventually being incorporated into bed nets.[6] Mosquitoes are one of the creatures that can act as disease carriers to humans. These diseases can later be transmitted to different places through human travel. For example, they can be transferred to an area where the disease did not exist before and then spread and cause health, economic, etc. problems. For this reason, we investigated a number of these diseases and the role of mosquitoes in their transmission and infection, as well as how to control and manage them.

Table 1. Impact of Mosquitoes on Human Health

Aspect	Description
Transmission of Diseases	Mosquitoes act as vectors for numerous pathogens, including viruses (e.g., Dengue, Zika, Chikungunya), parasites (e.g., malaria), and filarial worms, transmitting them to humans during blood feeding.
Nuisance Factor	Mosquitoes cause discomfort and nuisance to humans, especially in temperate regions during seasonal outbreaks, impacting outdoor activities, tourism, and outdoor labor.
Vector Competence	Mosquitoes exhibit varying degrees of vector competence, influenced by factors such as longevity, body size, and biting frequency, which affect the dynamics of pathogen transmission.
Mosquito Saliva	Mosquito saliva, containing over 100 proteins, facilitates blood feeding by counteracting vasoconstriction, platelet aggregation, and inflammation. However, it can also enhance the pathogenicity of arboviruses and influence the human immune response.
Public Health Concerns	Mosquito-borne diseases pose significant public health concerns globally, necessitating vector control measures and research into disease prevention and management.

Method

PubMed, Embase and Web of Science databases were searched for the keywords Mosquito, Malaria, Zika, Chikungunya, Dengue, Dengue fever and Vector-borne until 2020.

Mosquito and human health: investigating the hidden life of this insect

The Culicidae family, originating from culex, the Latin term for "gnat," belongs to one of the primary stocks of Nematocera, within the infraorder Culicomorpha. It comprises two superfamilies encompassing all piercing/sucking nematocerans, including both predators and blood-feeding biters. The superfamily Chironomoidea includes the Chironomidae and Thaumaleidae families, with nonpiercing mouthparts, as well as Simuliidae and Ceratopogonidae, which pierce either vertebrates or invertebrates. The superfamily Culicoidea consists of Dixidae, Corethrellidae, Chaoboridae, and Culicidae, the latter two of which feed on vertebrate blood. Culicidae encompasses approximately 3,500 recognized species. Most mosquito eggs are elongated, ovoid, or spindle-shaped, with some being spherical or rhomboid. The outer layer of the egg shell, or chorion, often exhibits intricate surface structures and patterns specific to the species. Anopheles species' chorions feature unique, transparent air-filled compartments flanking the egg, serving as floats. Eggs of Anopheles, Toxorhynchites, Wyeomyia, Aedes, Psorophora, and Haemagogus spp. are laid individually, while those of Culex, Culiseta, Coquillettidia, and Mansonia spp. are attached in a single clump, forming a floating egg raft or submerged cluster. Culex eggs possess a cup-shaped corolla at one end, allowing them to sit vertically on the water surface in a raft, with upper ends bearing apical droplets thought to maintain the raft's upright position chemically. Mosquito larvae, commonly known as wigglers or wrigglers, progress through four instars, closely resembling one another except for size differences. Adult mosquitoes are slender, with thin legs and narrow, elongated wings. Their body surface is adorned with scales, setae, and fine pile, defining the characteristic markings and colors of each species. The holometabolous life cycle of mosquitoes unfolds in two distinct environments: aquatic and terrestrial. Larvae and pupae develop in various aquatic habitats, with the key requirement being the maintenance of at least a water film throughout the larval and pupal stages.[3] Upon emergence from the pupa, one of the initial tasks for a mosquito is to seek out a sugar source. Carbohydrates play a vital role in meeting the mosquitoes' daily energy needs, with males relying entirely on sugar feeding. Nectar serves as the primary sugar source, although mosquitoes may also feed on fruits, honeydew, or extra-floral nectar.[7,8] Mosquitoes, like other Diptera, possess the unique ability to mate while in flight.[7,9] Mating can occur within swarms formed by males, particularly in most anopheline species, while both males and females may also gather near emergence sites or around vertebrate hosts, predominantly in culicine species.[7,10] Water is essential for all mosquitoes to complete their life cycle, although certain species require minimal water and can develop in a thin moisture film. The mosquito life cycle exemplifies complete metamorphosis, comprising four distinct stages: egg, larva (aquatic feeders), pupa (aquatic non-feeders), and adult. Similar to most insects undergoing complete metamorphosis, mosquitoes exhibit developmental stages that differ significantly in appearance from one another.[11]

Effects of mosquitoes on humans

Mosquitoes profoundly impact the health and quality of life for human populations due to two primary factors: the transmission of mosquito-borne diseases and the irritation caused by mosquito bites. In temperate regions, seasonal surges in mosquito populations result in nuisance in recreational and residential areas. Mosquitoes are commonly perceived as detrimental to human well-being as they impede outdoor activities and can also have adverse effects on the economy by deterring tourism and outdoor labor.[12] Mosquitoes serve as hematophagous vectors for numerous pathogenic viruses responsible for human diseases. These viruses maintain a life cycle between mosquitoes and vertebrate animals in nature. When a mosquito feeds on an infected host, it acquires viruses through blood meals, allowing the viruses to proliferate within the mosquito's tissues. Subsequently, the infected mosquito becomes a reservoir for the virus and can transmit it to naive vertebrate hosts during subsequent blood meals. To thrive and cycle between these two distinct host environments, mosquito-borne viruses have evolved sophisticated strategies to exploit various host and vector factors effectively. In their natural cycle, mosquito-borne viruses circulate between mosquitoes and vertebrate animals. When a mosquito feeds on a virus-infected host, it inadvertently ingests viruses present in the host's bloodstream. These viruses then establish infection in the mosquito's epithelial cells, overcoming physical and immune barriers, before spreading into the mosquito's body cavity (haemocoel). From there, the viruses infect other tissues such as the salivary glands, ovaries, and neural system. Consequently, the infected mosquito becomes capable of transmitting the viruses to naive hosts during subsequent blood meals. Throughout their life cycle, these viruses employ various strategies to exploit mosquito biology, enabling efficient carriage and transmission.[5] Mosquitoes play a significant role in transmitting numerous parasites and pathogens, including viruses from families such as Flaviviridae, responsible for diseases such as Dengue, West Nile fever, yellow fever, and Zika, as well as Togaviridae, which includes viruses like Chikungunya and Mayaro. Additionally, mosquitoes act as vectors for parasites such as malarial parasites and filarial worms (e.g., Dirofilaria). The primary vectors of these pathogens are often mosquitoes belonging to the genera Aedes, Anopheles, and Culex. Various factors, including the longevity, body size, and biting frequency of infected mosquitoes, significantly influence the dynamics of pathogen transmission. These traits are heavily influenced by the availability of food resources.[13] Mosquito saliva is a highly intricate blend containing over 100 proteins, many of which possess unidentified functions. This complex mixture enables mosquitoes to obtain a blood meal from their hosts, which is essential for egg maturation, by evading vasoconstriction, platelet aggregation, coagulation, and inflammation or hemostasis processes. During the acquisition of a blood meal, mosquitoes inject various salivary proteins into the host's skin. Previous research has indicated that mosquito saliva can amplify the pathogenicity of infections caused by dengue, West Nile, and other arboviruses. Research findings indicate that the human immune response to mosquito saliva is both significant and complex. Mosquito saliva has been found to alter the frequencies of several immune cell populations across multiple tissues, at various time points following blood feeding. Additionally, mosquito saliva influences serum cytokine levels, with a notable trend being an increase in anti-inflammatory and Th2 cytokines compared to control mice that were not bitten, particularly evident at 7 days post-bite. The duration of these effects, lasting up to 7 days post-bite, is particularly noteworthy and raises concerns regarding potential allergic reactions. The prolonged effects observed in humanized bone marrow and skin cells could potentially explain how certain viruses transmitted by mosquitoes may remain viable in these tissues or serve as replication reservoirs. Furthermore, it has been demonstrated that mosquito saliva elicits a mixed Th1/Th2 response.[2]

Investigating the mechanism of disease transmission by mosquitoes

The emergence and escalation of both new and established vector-borne diseases pose an increasingly serious threat to global public health. Currently, eighty percent of the world's population is at risk of contracting vector-borne diseases. Despite substantial advancements in malaria control, the disease still claims over 400,000 lives annually. Dengue, the most prevalent mosquito-borne viral illness, poses a significant threat to hundreds of millions of people each year, despite considerable control efforts. Moreover, significant outbreaks of other mosquito-borne diseases, such as chikungunya, West Nile virus, and Zika virus, further contribute to the escalating public health burden. For vector-borne pathogens, bites from vectors play a crucial role in transmission, and the rate of contact between hosts and vectors consistently emerges as the most critical parameter determining disease risk, as evidenced by studies utilizing mathematical models.[14] Many mosquito-borne diseases are categorized as emerging or reemerging, as is the case with dengue virus (DENV) fever. Incidence of dengue fever has shown a dramatic increase over the last few decades, spreading to areas of Africa, America, Asia, and Oceania that were previously unaffected. Similarly, chikungunya virus (CHIKV) was initially identified in 1952, with outbreaks primarily confined to Africa and Asia until 1973. However, since 1999/2000, significant outbreaks of chikungunya virus have occurred in tropical and subtropical regions of Africa, Asia, and Oceania.[15] Global forces from climate change to surging worldwide air travel are contributing to the globalization of vector-borne diseases such as West Nile virus, dengue and chikungunya.[16]

Malaria

From 1963 to 2001, a total of 185 deaths attributed to imported malaria were reported in the United States. The most common symptom observed in returned travelers with malaria is fever, often accompanied by influenza-like symptoms.[1] Malaria is a vector-borne blood disease caused by protozoan parasites belonging to the genus Plasmodium. Following transmission to humans through the bite of an infected female Anopheles mosquito, the parasites undergo initial multiplication in the liver before progressing to the pathogenic blood stages. These blood-stage infections can persist for months, and only once the sexual precursor cells, known as gametocytes, have matured, can the malaria parasites leave the human host and continue their life cycle within the insect vector.[17] Malaria is spread through the bite of infectious female Anopheles mosquitoes, highlighting the importance of understanding mosquito ecology and population dynamics in devising effective strategies to combat the disease. Fundamental factors such as vector ecology play a critical role in shaping transmission patterns, and alterations in land usage or modification can significantly impact transmission rates, either positively or negatively. A prime illustration of this dynamic is the ongoing urbanization trend in Africa, which has profound implications for malaria transmission.[18] Among the five Plasmodium species known to cause malaria in humans, Plasmodium falciparum is particularly lethal and accounts for severe disease pathology and the majority of malaria-related deaths, particularly in sub-Saharan Africa. On the other hand, Plasmodium vivax generally causes milder infections compared to P. falciparum but has a much wider geographical distribution. The clinical manifestations of malaria primarily result from the replication of asexual stages within the human bloodstream, while transmission to mosquitoes occurs only following the development of sexual stages, known as gametocytes. The duration required for gametocyte maturation varies significantly among different Plasmodium species. For instance, it takes approximately 8-10 days for a P. falciparum gametocyte to mature through five distinct morphological phases (stages I-V). P. vivax gametocytes, require around 48 hours to develop and typically disappear from circulation within 3 days following sexual maturation. In rodent malaria parasites such as Plasmodium berghei and Plasmodium yoelii, gametocyte maturation takes only 24-27 hours.[19] Plasmodium vivax and Plasmodium falciparum are responsible for the vast majority (>90%) of human malaria infections globally, and both can only be transmitted from one human to another via mosquitoes. The entire infectious reservoir for these critically important pathogens is exclusively found in humans, necessitating that a mosquito must bite at least two individuals during its lifetime for transmission to occur.[20] Epidemiological approaches to malaria have focused on two primary clinical syndromes: severe malarial anaemia and cerebral malaria. Typically, the mean age of children with severe malarial anaemia is lower than that of those with cerebral malaria within a given area. In regions with higher malaria transmission rates, children tend to encounter malaria at a younger age, resulting in a lower mean age for clinical cases overall. Consequently, malarial anaemia tends to be relatively more significant in high-transmission settings, while cerebral malaria gains prominence in areas with lower transmission rates.[21] While temporary movements, primarily associated with business, holidays, or social visits, may contribute to small-scale outbreaks in malaria-free areas, long-term and continuous migration can significantly impact observed and stable malaria transmission dynamics.[22] The movement of infected individuals from regions where malaria is still endemic to areas where the disease has been eradicated has led to the resurgence of malaria in some cases. However, population movement can also precipitate or exacerbate malaria transmission in other ways. As people migrate, they may increase their risk of acquiring the disease by altering the environment and introducing new technologies. For instance, activities such as deforestation and the implementation of irrigation systems can create favorable conditions for mosquito breeding and malaria transmission.[23, 24] A study was conducted to investigate the relationship between malaria transmission, infection, and disease at three sites in Uganda with varying levels of transmission intensity. This research benefited from a comprehensive understanding of the study sites, dynamic cohorts comprising participants who all received long-lasting insecticidal nets (LLINs) and prompt treatment of malaria with artemisinin-based combination therapies (ACTs), as well as entomological data collected from households where cohort members resided. The study revealed several key findings:

1. Highly seasonal transmission patterns were observed, with varied relationships between measures of transmission, infection, and disease.
2. There was a decrease in malaria incidence in the peri-urban site, while high and increasing incidence rates were observed in the two rural sites.
3. Severe disease incidence was found to be very low across all sites.
4. Prevalence of anemia was low and decreasing at all study sites.[25]

Zika fever

Zika virus (ZIKV) is a 50-nm enveloped virus with an inner nucleocapsid and an outer lipid bilayer. Its inner nucleocapsid consists of a linear positive-sense, single-stranded RNA virus measuring 10,794 nucleotides in length, along with multiple copies of the viral capsid protein.[26] ZIKV belongs to the family Flaviviridae and the genus Flavivirus. The virus was initially isolated in 1947 from a sentinel rhesus monkey in the Zika Forest in Uganda and subsequently from Aedes africanus mosquitoes in the same forest in 1948, indicating mosquito-borne transmission of the virus. Currently, various pieces of evidence point to the mosquito Aedes aegypti as the primary vector of ZIKV, as this species has been demonstrated to be capable of transmitting the virus. Aedes aegypti is also the primary vector of other arboviruses such as DENV, CHIKV, and Yellow fever virus. Urbanization plays a significant role in facilitating the proliferation of Aedes aegypti populations. This is primarily due to the increase in human-made containers used to store water in and around inhabited areas, which serve as the aquatic larval environment required by these mosquitoes.[27] The emergence of ZIKV has been linked to the description of severe neurological complications, including Guillain-Barré syndrome (GBS) in adults in French Polynesia and microcephaly in neonates in Brazil. It has become evident that ZIKV is following a similar pattern to other arboviruses like DENV and CHIKV, spreading to countries where Aedes aegypti and Aedes albopictus mosquitoes are present. Traditionally, a vector of arboviruses is defined as an arthropod that transmits the virus from one vertebrate host to another through a bite. However, non-vector transmission of arboviruses has also been reported, including direct transmission between vertebrates, from mother to child, nosocomially (in healthcare settings), through transfusion, via bone marrow or organ transplantation, and sexually.[28] While Zika virus disease is primarily considered a vector-borne disease, cases of sexual transmission and congenital transmission have been reported.[29] The findings of a study have revealed that the three most prevalent Culex taxa in central Europe (Cx. p. pipiens, Cx. p. molestus, and Cx. torrentium) do not exhibit vector competence for ZIKV.[30] ZIKV strains can be categorized into three main lineages: East African, West African, and Asian. The primary mode of ZIKV transmission to humans is through the bite of infected mosquitoes. There are two main transmission cycles:

1. Sylvatic cycle: This cycle occurs between non-human primates and arboreal canopy-dwelling mosquitoes, such as Ae. africanus and Ae. bromeliae.
2. Urban cycle: In this cycle, humans serve as both reservoir and amplification hosts, and anthropophilic mosquitoes act as vectors. The primary vectors are Aedes aegypti, with Aedes albopictus playing a secondary role.

ZIKV, like many arboviruses, has the potential to persist in mosquito eggs. Vertical transmission of the virus to offspring can occur through two mechanisms:

1. Transovarial transmission: The virus infects germinal tissues in the ovaries.
2. Trans-egg transmission: Infection occurs during fertilization.

Vertical transmission has been demonstrated in Aedes aegypti and Aedes albopictus mosquitoes. Venereal transmission is another mechanism through which the virus can spread within a mosquito population. While males cannot acquire the virus from a blood meal, they can acquire it through vertical transmission from an infected female parent. Experimental studies have shown that infected male Ae. aegypti can horizontally transmit the virus to non-infected adult females during mating.[26] Studies have demonstrated that ZIKV can be transmitted by a wide range of mosquito species; however, five vectors (Ae. furcifer, Ae. taylori, Ae. luteocephalus, Ae. vittatus, and Ae. africanus) appear to play the most significant roles in transmission. While ZIKV primarily circulates in sylvatic habitats, it has been isolated in urban settings from humans and Aedes aegypti mosquitoes in Africa and Asia.[31] Many individuals infected with ZIKV either remain asymptomatic or develop a mild illness characterized by fever, headache, malaise, arthralgia, conjunctivitis, and a maculopapular rash. Despite the seemingly mild nature of the viral syndrome, concern has arisen due to observations of mother-to-child transmission during pregnancy, leading to microcephaly and other congenital deformities in infants, as well as miscarriages. Additionally, cases of GBS have been diagnosed as a complication of ZIKV infection.[32] In early 2016, a number of sexually transmitted cases of ZIKV infection from males to females were documented in the United States.[32,33] The women who contracted the disease through sexual transmission did not have any history of travel to affected areas. However, their male partners had traveled to countries where the Zika virus is present. The onset of symptoms in these women occurred within 2 weeks of their male partners experiencing symptoms. These cases highlight not only a mode of transmission other than through a mosquito vector but also suggest a possible post-infection carriage state in human semen. Prior to the documentation of Zika transmission through sexual intercourse in the United States, scientists in Tahiti confirmed the presence of the virus in the semen of a man for 2 weeks or more after he had recovered from a second bout of the disease.[32, 34] Air, land, and sea transportation can facilitate the rapid spread of infectious diseases.[35]

Chikungunya

CHIKV was initially discovered in 1953 when it was isolated from a febrile patient's blood in Tanzania. Belonging to the genus Alphavirus within the Togaviridae family, this virus features a single-stranded RNA genome, encapsulated within a 60- to 70-nm diameter capsid, and enveloped by a phospholipid membrane.[36] Its endemic regions include sub-Saharan Africa as well as South and East Asia. However, in recent times, instances of chikungunya have emerged beyond its traditional territories due to the rise in international travel. Following an average incubation period spanning 3-7 days (with a range of 2-12 days), individuals infected with CHIKV enter a viremic state. Among those who exhibit symptoms, typical manifestations include fever, headache, rash, and severe symmetrical polyarthralgia. The period of highest risk for transmission from an infected individual to a susceptible Aedes mosquito occurs within the initial 2-6 days of illness, coinciding with the viremic phase.[16]

CHIKV primarily spreads through the bite of Aedes aegypti and Ae. albopictus mosquitoes, which are also responsible for transmitting dengue and Zika viruses. Humans serve as the main amplifying host for the chikungunya virus, as they reach sufficiently high levels of viremia to infect mosquitoes that feed on them. Consequently, infected individuals traveling to nonendemic regions can inadvertently introduce the virus, potentially triggering local transmission and outbreaks of the disease.[37] The initial urban outbreaks of chikungunya in Bangkok, Thailand, occurred during the early 1960s.[38] The global spread of CHIKV has been facilitated by the migration of infected individuals to regions harboring competent mosquito vectors and susceptible human populations. Cases of CHIKV infection among travelers have been documented in over 22 countries across Asia, Europe, and North America. Three distinct genotypes of CHIKV—East-Central-South African, West African, and Asian—have been identified, suggesting independent evolutionary pathways in different geographic regions. Ae. aegypti and Ae. albopictus mosquitoes are capable vectors for the Asian genotype of CHIKV. Chikungunya virus shares a similar urban epidemic transmission pattern with DENV, utilizing Ae. aegypti and Ae. albopictus as vectors. Similar to dengue, epidemic chikungunya is classified as an anthroponosis, and does not rely on a nonhuman vertebrate amplifier host.[39] The primary vectors responsible for transmitting CHIKV are Aedes aegypti and Aedes albopictus mosquitoes. Aedes albopictus, in particular, exhibits remarkable adaptability:

1. It can thrive across a wide geographic range, spanning both urban and rural environments.
2. Its eggs possess a remarkable ability to resist desiccation, allowing them to endure throughout dry periods until the onset of rainy seasons.
3. This mosquito species is characterized by its quiet and diurnal behavior, rendering conventional measures like bed nets ineffective in controlling its population.

Advancements in molecular techniques have significantly improved the reliability of CHIKV detection. The virus can be identified through serological assays or reverse transcription (RT)-PCR. Immunoglobulin M (IgM) becomes detectable approximately two days after the onset of symptoms through enzyme immunoassay (EIA) testing and can persist for up to three months. IgG, on the other hand, becomes detectable around 15 days post-symptom onset and can remain detectable for years. However, it's worth noting that these serological tests may yield false-positive results due to cross-reactivity with other viruses such as DENV and O'nyong-nyong virus. Evidence suggests that CHIKV infection confers lifetime immunity in individuals. Moreover, animal studies have demonstrated cross-protection against other arboviruses.[36] While the majority of CHIKV transmission is through mosquito bites, there are instances of vertical transmission from a pregnant woman to her infant during childbirth (known as perinatal transmission). This mode of transmission occurs regularly and can result in severe central nervous system disease in the newborn, which may sometimes prove fatal. Additionally, vertical transmission among mosquitoes has also been documented.[40] In the vast majority of cases, CHIKV infection manifests with a sudden onset of fever, often accompanied by joint pain as a prominent symptom. While other symptoms may also occur, they are typically less pronounced and may include debilitating polyarthralgia and arthritis, rash, muscle pain (myalgia), and headache. CHIKV infecting various cell types within the body. These include dendritic cells, macrophages, synovial fibroblasts, endothelial cells, and myocytes. In humans, CHIKV has been observed to infect osteoblasts as well, contributing to the joint damage and erosive disease observed in individuals with chronic arthritis. Recent studies have also detected CHIKV RNA and antigens in the spleen, lymph nodes, liver, and muscle tissue of experimentally infected macaques up to 90 days post-infection.[41]

Dengue fever

The worldwide spread of DENV has undergone a significant expansion, propelled by factors such as rapid urbanization, increased international travel, insufficient mosquito control measures, and globalization trends. The viral genome of DENV comprises a positive-sense RNA molecule of approximately 11 kilobases in length. The RNA of DENV is translated into a single polyprotein that is responsible for encoding three structural proteins: capsid (C), premembrane (prM), and envelope (E). Additionally, it encodes for seven nonstructural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. Visualization through three-dimensional reconstruction techniques reveals that mature DENV particles exhibit a diameter of approximately 50 nanometers. The virus is composed of an outer protein shell (E and M), a lipid bilayer, and a less characterized nucleocapsid core (C and RNA genome).[42] There are two species of Aedes mosquitoes, namely Aedes aegypti and Aedes albopictus, that play a crucial role in the transmission of the dengue virus. These mosquitoes can be distinguished based on their physical characteristics: both species have a black coloration, but they can be easily identified by examining the pattern of white scales on their dorsal thorax. Ae. aegypti typically displays two straight lines bordered by curved lyre-shaped lines, while Ae. albopictus exhibits a single broad line of white scales across the middle of the thorax. Adult female Aedes mosquitoes engage in mating, blood-feeding, and egg-laying activities. They deposit around 60–100 eggs in both artificial and natural containers and have an average lifespan of 20–30 days. Aedes mosquitoes are known to be daytime biters, with peak biting activity occurring during dawn after sunrise and at dusk before sunset. When an Aedes mosquito ingests the dengue virus from an infected individual, the virus undergoes a period of multiplication within the mosquito's salivary glands, lasting approximately 8–10 days (known as the incubation period). Subsequently, during subsequent blood meals, the virus can be transmitted to another person through mosquito bites. The flight range of Aedes mosquitoes is relatively limited, typically ranging from 50 to 200 meters from their breeding sites.[43] Dengue viruses are classified into four antigenically distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. These viruses can be transmitted to humans through the bite of an infected female Aedes mosquito, a process known as horizontal transmission. Upon feeding on a blood meal, the virus attaches to various cellular receptors and enters midgut cells of the mosquito host via cell-mediated endocytosis. Subsequently, the viruses disseminate systemically through the haemocoel or body cavity to other secondary tissues, including the salivary glands.[43,44] In addition to horizontal transmission, natural vertical transmission of dengue viruses from infected females to their offspring has been documented in many dengue-endemic regions.[43,45] Dengue Fever is recognized as an endemic or epidemic disease in approximately 119 countries worldwide, with a significant portion of them located in Asia. The occurrence and spread of Dengue Fever are influenced by various risk factors, including the presence and virulence of the dengue virus, the behavior and capacity of mosquitoes as vectors, climate or weather conditions, human immunity levels, and human activity patterns. However, research indicates that climate factors exert a particularly notable impact on Dengue Fever compared to other factors. The abundance of sunlight and precipitation during summer creates optimal breeding sites for mosquitoes, thus fostering favorable conditions for Dengue fever transmission. Recent studies have suggested that global warming exacerbates the prevalence of Dengue fever by introducing warmer and wetter spring and winter seasons, which are conducive to the proliferation of both the DENV and mosquito populations. Climate factors interact with Dengue Fever incidence and distribution in a complex manner, with anthropogenic influences further complicating the situation. Imported cases of Dengue Fever resulting from human activities such as travel pose an additional threat, particularly in regions with favorable weather conditions for virus transmission.[46] Interrupting the transmission of pathogens by controlling mosquito populations stands out as the most effective approach to controlling dengue infection.[47] The transmission of the virus from infected humans to mosquitoes represents a crucial stage in dengue epidemiology. However, due to logistical challenges, this process has only been directly examined in a limited number of studies. During the initial experimental infections of human volunteers in the 1920s, clinical symptoms typically appeared 4–9 days after virus inoculation via mosquito bite. Infected individuals were found to be infectious to mosquitoes from 2 days before to 2 days after the onset of symptoms. Furthermore, Ae. aegypti mosquitoes that fed on viremic individuals were capable of transmitting the virus to another person after an extrinsic incubation period of at least 11 days. Subsequent studies revealed that in naturally infected individuals with clinically apparent dengue, detectable viremia typically lasted for an average of 4–5 days after symptom onset, but could range from 2 to 12 days.[48] The spectrum of disease symptoms associated with dengue fever varies from asymptomatic or mild cases to severe stages such as dengue hemorrhagic fever and dengue shock syndrome.[49] Dengue fever is commonly characterized by a rapid onset of fever, headache, rash, and intense joint and muscle pain.[50]

A way to prevent and manage

Malaria has been a longstanding issue in continental Europe, but it was successfully eliminated in the 1970s through a combination of strategies. These strategies included early detection and treatment of cases, control of mosquito vectors through indoor residual spraying of houses and larviciding of breeding sites, environmental modifications, and adjustments to human habitats.[4]

The World Health Organization (WHO) recommends specific interventions for malaria control, with insecticide-treated nets (ITNs) and indoor residual spraying (IRS) typically being the primary preventive measures employed. Effective case management is also crucial, and distribution of LLINs is often implemented, with priority given to vulnerable populations such as pregnant women and children under 5 years old. The overarching goal is to achieve and sustain universal community-level coverage of these interventions.[51] The use of LLINs and IRS has played a pivotal role in achieving significant reductions in malaria burden during the twenty-first century.[6] In the late 1950s, the United States Agency for International Development (USAID) provided DDT to India, leading to a remarkable decline in malaria prevalence. This intervention resulted in a substantial reduction in the number of annual malaria cases in India, from an estimated 100 million in the early twentieth century to around 100 thousand cases by 1965. Prevention of re-establishment (POR) strategies are aimed at preventing the occurrence of malaria outbreaks or the re-establishment of indigenous malaria in countries that have achieved malaria elimination. The WHO has outlined essential guidelines for POR, which include:

1. Implementing an efficient malaria surveillance system.
2. Maintaining POR budgets at least at the same level as pre-elimination efforts.
3. Continuing education and training programs for general health services personnel to ensure proficiency in malaria diagnosis, treatment, and vigilance.
4. Training new healthcare personnel in malaria diagnosis and treatment.
5. Establishing or maintaining region-specific malaria prevention services based on epidemiological data sources.[52]

Management of dengue fever primarily involves supportive care, including fluid replacement or resuscitation as needed. In cases of dengue hemorrhagic fever, blood transfusions may be necessary. Fever can be managed with acetaminophen, although salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided due to the heightened risk of bleeding. Salicylates, in particular, may also be associated with Reye's syndrome, especially in children.[1] For the control of CHIKV outbreaks, the main strategy involves suppressing vector populations, utilizing individual protective measures such as repellents, and reinforcing epidemiological surveillance in high-risk epidemic areas. Ambient temperatures, as well as daily fluctuations in temperature, play a crucial role in influencing the competence of mosquito vectors for pathogens. Additionally, research has demonstrated that the potential for CHIKV transmission by Ae. albopictus is heavily influenced by the interaction between mosquito population, virus strain, and temperature.[53] To mitigate further transmission of the chikungunya virus, it is advisable to keep patients under mosquito netting while they are febrile. Treatment mainly involves supportive care, including rest, adequate fluid intake, and management of fever using acetaminophen. Similar to dengue fever, salicylates should be avoided in children due to the risk of Reye's syndrome, but NSAIDs may be cautiously used if acetaminophen is insufficient, as there is limited risk of hemorrhagic complications with chikungunya fever.[1] In areas affected by ZIKV, the prevalence of antibodies against DENV is often high, posing challenges in serologically distinguishing between ZIKV and DENV infections. Recent research suggests that immunity to DENV can provide protection against ZIKV. Despite significant efforts directed toward diagnosis, treatment, and vaccine development for ZIKV infections, no vaccines have yet been approved for public use.[54] Given the lack of approved vaccines for CHIKV and ZIKV, prevention and control efforts primarily rely on public awareness and implementation of preventive measures to curtail the spread of both mosquitoes and the diseases they transmit. These measures include eliminating breeding sites and protecting against mosquito bites.[55]

Conclusion

Understanding the intricate relationship between mosquitoes and human health is paramount for effective disease control and prevention strategies. Investigating the mechanisms of disease transmission by mosquitoes is essential for understanding the dynamics of mosquito-borne diseases and developing targeted interventions (Table 2). By addressing the complex interactions between mosquitoes, pathogens, and human hosts, we can enhance disease surveillance, prevention, and control efforts on a global scale. Malaria and Zika fever represent significant challenges to global health, with complex transmission dynamics influenced by vector ecology, human behavior, and environmental factors. Understanding these dynamics is critical for the development and implementation of effective control measures and public health interventions aimed at reducing the burden of these diseases worldwide. Continued research and surveillance are essential to monitor transmission patterns, identify emerging threats, and inform evidence-based strategies for disease prevention and management. Chikungunya and dengue fever represent significant challenges to global public health, requiring comprehensive strategies for prevention and management. By focusing on vector control, individual protections, surveillance, and supportive care, we can mitigate the impact of these diseases and reduce transmission rates. Continued efforts in research and vaccine development are essential for long-term control and prevention.

Table 2. Comparison of Vector-Borne Diseases

Disease	Pathogen	Vector(s)	Transmission	Symptoms
Malaria	Protozoan parasites (Plasmodium)	Female Anopheles mosquitoes	Mosquito bites	Fever, influenza-like symptoms, severe pathology, anemia, cerebral malaria
Zika Fever	Zika virus (ZIKV)	Aedes mosquitoes (primarily Aedes aegypti and secondarily Aedes albopictus)	Mosquito bites, sexual, congenital	Fever, headache, malaise, arthralgia, conjunctivitis, rash, microcephaly (in infants), Guillain-Barré syndrome
Chikungunya	Chikungunya virus (CHIKV)	Aedes mosquitoes (primarily Aedes aegypti and Ae. albopictus)	Mosquito bites	Fever, headache, rash, polyarthralgia, arthritis, central nervous system disease, congenital deformities (in infants)
Dengue Fever	Dengue virus (DENV)	Aedes mosquitoes (primarily Aedes aegypti and secondarily Aedes albopictus)	Mosquito bites	Fever, headache, rash, severe joint and muscle pain, dengue hemorrhagic fever, dengue shock syndrome

Note: Symptoms and transmission methods vary between diseases, with some diseases capable of sexual and congenital transmission in addition to mosquito-borne transmission.

Highlights

What Is Already Known?

Urbanization facilitates the proliferation of Aedes populations, exacerbating viral transmission. Chikungunya, spread by Aedes mosquitoes, has expanded beyond endemic regions due to international travel, causing fever, rash, and joint pain. Dengue fever, caused by dengue viruses transmitted by Aedes mosquitoes, witnesses a global resurgence, with climate factors influencing disease transmission dynamics.

What Does This Study Add?

Effective mosquito control strategies are essential for mitigating the impact of these vector-borne diseases on global health.

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Conflict of Interest

The authors have no conflict of interest to declare.

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