**REVIEW**
DOI: https://doi.org/10.36233/0507-4088-209


# Current Diagnostics and Biomarkers for Arboviral Infections (a Review on Dengue, Zika, West Nile and Chikungunya Viruses)

Hafeez A. Adekola✉, Kareem A. Wahab, Omotayo E. Odunsi, Tobiloba A. Abesin, Oluwaseun A. Oyesanya

Department of Microbiology, Olabisi Onabanjo University, Ago Iwoye, Nigeria

**Abstract**
Arboviral infections, transmitted to humans primarily through arthropod vectors, constitute a significant global health threat. Arboviruses, such as Dengue, Zika, Chikungunya, and West Nile viruses, continue to cause widespread outbreaks, necessitating advanced diagnostic tools. Emerging technologies including Lab On A Chip (LOC), Lab On A Disc (LOAD), Microfluidic Paper-Based Analytical Devices (μPADS), Lateral Flow Devices, CRISPR-CAS 12/13, Quartz crystal microbalance (QCM), and Nano-Technology are evaluated for their potential to enhance arboviral diagnosis, offering rapid, accurate, and point-of-care solutions. Furthermore, the identification of robust biomarkers, including Inflammatory Cytokines, Antibodies, Endothelial Activation Products and Indicators of Tissue or Organ Damage, is crucial for improving the understanding of disease pathogenesis, prognosis, and treatment response. A comprehensive analysis of potential diagnostics and biomarkers for arboviral infections sheds light on the evolving strategies to combat these medically significant diseases, ultimately contributing to more effective surveillance, diagnosis and management worldwide.

**Keywords:** *Diagnostics; Biomarkers; Zika; Dengue; West Nile; Chikungunya*

**For citation:** Adekola H.A., Wahab K.A., Odunsi O.E., Abesin T.A., Oyesanya O.A. Current Diagnostics and Biomarkers for Arboviral Infections (A Review On Dengue, Zika, West Nile And Chikungunya Viruses). *Problems of Virology* (*Voprosy Virusologii*). 2024; 69(1): 31–41. DOI: https://doi.org/10.36233/0507-4088-209 EDN: https://elibrary.ru/xtgvns

**Funding.** This study was not supported by any external sources of funding.
**Conflict of interest.** The authors declare no apparent or potential conflicts of interest related to the publication of this article.

**НАУЧНЫЙ ОБЗОР**
DOI: https://doi.org/10.36233/0507-4088-209

# Современная диагностика и биомаркеры арбовирусных инфекций (обзор вирусов денге, Зика, Западного Нила и чикунгунья)

Adekola H.A.✉, Wahab K.A., Odunsi O.E., Abesin T.A., Oyesanya O.A.

Факультет микробиологии, Университет Олабиси Онабанджо, Аго-Ивойе, Нигерия

**Резюме**
Арбовирусные инфекции, передающиеся человеку в основном через членистоногих переносчиков, представляют собой значительную глобальную угрозу здоровью населения. Арбовирусы, такие как вирусы денге, Зика, чикунгунья и Западного Нила, продолжают вызывать широкомасштабные вспышки заболеваний, что требует применения современных средств диагностики. Новые технологии, такие как «Лаборатория на чипе» (LOC), «Лаборатория на диске» (LOAD), микрофлюидические аналитические устройства на бумажной основе (μPADS), иммунохроматографический анализ (ИХА), CRISPR-CAS 12/13, кварцевые микровесы (QCM) и нанотехнологии, оцениваются с точки зрения их потенциала для улучшения диагностики арбовирусов, поскольку они предлагают быстрые, точные и точечные решения. Кроме того, выявление надежных биомаркеров, включая воспалительные цитокины, антитела, продукты активации эндотелия и индикаторы повреждения тканей или органов, имеет решающее значение для лучшего понимания патогенеза заболевания, прогноза и ответа на лечение. Всесторонний анализ потенциальных методов диагностики и биомаркеров арбовирусных инфекций проливает свет на развивающиеся стратегии борьбы с этими значимыми для медицины заболеваниями, что в конечном итоге способствует повышению эффективности надзора, диагностики и лечения во всем мире.

**Ключевые слова:** *диагностика; биомаркеры; вирус Зика; вирус денге; вирус Западного Нила; вирус чикунгунья*

**Для цитирования:** Adekola H.A., Wahab K.A., Odunsi O.E., Abesin T.A., Oyesanya O.A. Современная диагностика и биомаркеры арбовирусных инфекций (обзор вирусов денге, Зика, Западного Нила и чикунгунья). *Вопросы вирусологии*. 2024; 69(1): 31–41. DOI: https://doi.org/10.36233/0507-4088-209 EDN: https://elibrary.ru/xtgvns

**Финансирование.** Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.
**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

## Introduction

Arboviral infections (arthropod-borne viral infections) represent a category of viral diseases primarily transmitted to both humans and other animals through the bites of infected arthropods like mosquitoes, ticks, and sandflies [1]. These viruses exist within intricate cycles involving both arthropod vectors and vertebrate hosts [2]. Arboviral infections can provoke a broad spectrum of clinical symptoms, ranging from mild febrile illnesses to severe, potentially life-threatening conditions [3]. Arboviruses are transferred when an infected arthropod vector feeds on a susceptible host. The virus multiplies within the arthropod's body and subsequently enters the host's bloodstream when the feeding process happens. The infected host can exhibit symptoms and act as a source of infection for other vectors that feed on them [4].

The primary vectors responsible for arboviral transmission encompass mosquitoes, ticks, sandflies and midges [5]. Distinct arboviruses are associated with specific vector species. For instance, Aedes mosquitoes are recognized as transmitters of viruses such as dengue (DENV), Zika (ZIKV) and chikungunya (CHIKV), whereas Culex mosquitoes are vectors for West Nile virus (WNV) and Japanese encephalitis virus [6]. The distribution of arboviral infections is often influenced by the geographical range of these vector species [7]. Regions characterized by suitable climatic conditions and the presence of competent vectors are at a higher risk of experiencing outbreaks of these infections [8].

Symptoms of arboviral infections can vary widely but frequently include fever, headache, joint and muscle pain, rash and fatigue [9]. In more severe cases, these infections can lead to neurological complications, hemorrhagic fever, organ failure, and even death [10].

## Global burden of arboviral infections

the global burden of arboviral infections is substantial, with millions of cases reported annually [11]. Dengue fever alone affects over 100 countries, causing an estimated 390 million infections each year [12]. Similarly, ZIKV, CHIKV and WNV also contribute to this burden, affecting various regions [11]. The DENV infection places a significant global burden, with approximately 3.9 billion people across more than 120 countries at risk of contracting dengue [13]. Annually, there are about 100 million symptomatic cases, with approximately 500,000 severe cases requiring hospitalization [14]. Compared to other arboviral diseases such as dengue, the global burden of ZIKV infection is relatively lower [15]. However, it gained significant attention due to its association with birth defects, especially microcephaly, in babies born to infected mothers [16]. Notably, Zika outbreaks occurred in various regions, particularly in the Americas, from 2015 to 2016 [17]. Determining the exact number of ZIKV infections is challenging because many cases are asymptomatic or present with mild symptoms [18]. Nevertheless, during the outbreaks, thousands of cases were reported, and ZIKV transmission remains a concern, especially for pregnant women and their unborn children [19]. Since the early 2000s, multiple chikungunya outbreaks have been reported, particularly in regions with favorable mosquito habitats [20]. These outbreaks have resulted in significant morbidity, affecting both local populations and travelers [21]. However, quantifying the exact number of cases is challenging due to underreporting and misdiagnosis. WNV has been known to cause neurological conditions like encephalitis and meningitis since its discovery in the 1930s [22]. Most WNV infections, however, are asymptomatic or result in mild flu-like symptoms. The virus has been found in various bird species and can spread to humans through mosquito vectors [23]. Although the majority of WNV infections are mild, severe cases can lead to significant morbidity and mortality, particularly among older adults and individuals with weakened immune systems [23]. Presently, the global expansion of the WNV to colder regions is attributed to climate change [24]. Outbreaks of WNV infection, particularly linked to significant bird migration routes, have been documented in various countries, including Russia, the United States, Greece, Romania, Canada and others [24]. A typical instance can be found in the enduring endemic region located in southern Russia, specifically in the Volgograd region. This area continues to grapple with the impact of the WNV, exhibiting the highest recorded number of cases in the country [25].

These infections can result in severe illness, long-term health complications and even death [26]. Additionally, the economic impact is significant due to healthcare costs, lost productivity and resources dedicated to control measures [27].

## Potential diagnostics for arboviral infections

### *Lab On A Chip (LOC)*

Devices known as «lab on a chip» (LOC) handle all stages of the process, starting from sample purification and continuing through detection and result interpretation. The chemicals required for sample testing are of-

ten pre-loaded onto the instrument or contained in easily insertable cartridges on the platform, and these systems typically make use of microfluidics [28].

LOC devices have found utility in diagnosing various arboviral diseases. Velders et al. (2018) developed an affordable, battery-operated device for on-site ZIKV detection [29]. Sharma et al. (2020) engineered a microfluidic platform employing magnetic beads and LAMP to detect ZIKV in approximately 40 minutes [30]. Song et al. (2016) devised a simple disposable microfluidics cassette that can detect ZIKV in saliva samples in under 40 minutes [31]. Lastly, Ganguli et al. (2017) designed a microfluidics card combined with LAMP for the detection of ZIKV, DENV and CHIKV in whole blood samples. This system uses dried chemicals and offers a smartphone read-out [32]. Consequently, LOC devices are well-suited for field testing, point-of-care applications and the diagnosis of arboviruses in resource-limited settings.

*Lab On A Disc (LOAD)*

Similar to LOC (Lab-on-a-Chip) equipment, LOAD (Lab-on-a-Disc) devices perform various tasks including sample preparation, amplification, and result reading. LOAD relies on centrifugal forces, often coupled with microfluidics, as described by Wang et al. in 2021, and utilizes specific detecting agents, setting it apart from other techniques [33]. An example of a commercially available LOAD system is Diasorin's LIASON®MDX, which has been utilized for the identification of pathogens such as DENV, SARS-CoV-2, cytomegalovirus (CMV), herpes simplex virus (HSV) and Clostridium difficile, among others, as reported by Diasorin in Cyprus, CA, USA [34]. Furthermore, an INAAT-based LOAD system has been developed as a portable, closed, computer-controlled solution for detecting highly pathogenic avian influenza virus. This system consists of a low-cost centrifugal microfluidic cartridge and a compact, portable processing unit [34]. Another noteworthy development is the LOAD system designed by Strohmeier et al. (2015). This system, aimed at identifying the Rift Valley fever and yellow fever viruses, comprises a low-cost centrifugal microfluidic cartridge paired with a small, portable processing unit [35]. In recent times, Hin et al. (2021) introduced the FeverDisc, a fully integrated LOAD system utilizing LAMP technology. It can detect a wide range of pathogens, including *Plasmodium falciparum, P. vivax, P. ovale, P. malariae, Salmonella enterica Typhi, S. enterica Paratyphi A, Streptococcus pneumoniae*, CHIKV, DENV 1–4 and ZIKV. Users must manually add the sample into the cartridge, a process that takes approximately 5 minutes, and the results are generated within about 2 hours using lyophilized amplification reagents. Notably, this system eliminates the need for cold chain logistics, and although its price remains undisclosed, it is expected to be more cost-effective than existing methods [36].

*Microfluidic Paper-Based Analytical Devices (μPADS)*

The initial approach introduced in 2007 involves creating patterns of millimeter-sized channels on paper [37]. This method is both simple and cost-effective. Microfluidic Paper Analytical Devices (μPADs) typically consist of a combination of hydrophilic and hydrophobic microstructures deposited on paper. These structures enable the storage of reagents and the manipulation of samples within the μPAD, including sorting, mixing, and detection. These features make μPADs especially valuable for field testing and other Point-of-Care (POC) applications [28]. μPADs present an excellent alternative to conventional techniques for several reasons. They do not require a power source, are economical to produce and are easy to transport. Notably, they have been employed in the detection of ZIKV and CHIKV using NS1 protein-based μPADs, as well as CHIKV detection in less than 10 minutes using a laser-cut glass fiber μPAD [38]. Furthermore, wax barriers have been proposed to partition individual chambers within μPAD devices for use in a SARS-CoV-2 detection system linked to Loop-Mediated Isothermal Amplification (LAMP) amplification. These chambers include a sample zone, buffer zone, LAMP master mix zone, mixing zone and a sensor zone [39]. These cost-effective and straightforward methods can be applied to Point-of-Care settings to detect arboviral infections and other diseases.

*Lateral Flow Devices*

Since they have been utilized in POC applications for so long, lateral flow devices (LFDs) are perhaps the most popular platforms for the creation of such assays. Their wide use in POC development is a direct result of their affordability, usability, speedy results and straightforward interpretation. Heart illness, monitoring food toxins, food poisoning, bacterial infection, viral infection and many other conditions are examples of applications for LFDs [40–44].

Despite the fact that LFDs have been used widely for a long time, they typically lack the sensitivity and specificity of molecular techniques like RT-PCR and INAAT. Lateral flow detection has been used for the detection of various viral pathogens such as influenza virus, Japanese encephalitis virus, ZIKV, SARS-CoV-2, monkeypox virus, African swine fever virus and Heartland virus, LFDs have been coupled with LAMP and RPA amplification [40, 45–47].

*CRISPR-Cas 12/13*

Detection of pathogens through CRISPR-Cas technology relies on the inherent properties of CRISPR proteins. Bacteria employ a group of proteins called clustered regularly interspaced short palindromic repeats (CRISPRs) to execute an immune response, eliminating foreign DNA through sequence-specific RNA molecules known as crRNA [48]. Thanks to its intrinsic precision, the CRISPR-Cas9 system has found extensive utility in biology, both for genome editing and the identification of DNA and RNA molecules. This technique hinges on two catalytic domains, RuvC and HNH, which induce targeted cleavage at locations matching the guide RNA [49]. In contrast, the CRISPR-Cas12 system, unlike its Cas9 counterparts, employs a single catalytic domain, RuvC, to induce double-stranded DNA breaks, guided by crRNA. In order to trigger these breaks, Cas12a enzymes identify a T-rich protospacer adjacent motif (PAM) [50]. In this process, single-stranded DNA or RNA reporter mol-

ecules, potentially labeled with biotin or fluorescent tags, are introduced to generate a readable signal [48]. These assays, which include techniques like LAMP, RPA, HDA and SDA, have been integrated with isothermal nucleic acid amplification tests (INAAT) to produce cost-effective, field-deployable assays suitable for point-of-care (POC) applications. Notably, the CRISPR-Cas-12/13 systems have successfully detected various significant arboviruses, such as DENV, WNV, ZIKV, Japanese encephalitis virus, Crimean-Congo hemorrhagic fever virus and severe fever with thrombocytopenia syndrome virus to date [51–54].

*Quartz crystal microbalance (QCM)*

QCM is a label-free, very mass-sensitive device that uses the piezoelectric effect to detect binding events between minute amounts of medically relevant analytes and receptors on its surface [55]. Better sensitivity, usability, interaction with small analytical instruments, and economics are some of the benefits of QCM over other transducer types claimed [55]. In one study, a QCM-based immunochip was created to detect dengue viral antigens [56]. A piezoelectric transducer was coated with two distinct monoclonal antibodies that were utilized to identify DENV antigens in buffer [57]. The antibodies were directed against the glycoprotein-E and NS1 proteins, respectively [57]. The sensitivity was increased by multi-antibody coating, which enabled the collection of multiple antigens. Sensitivity was increased much more by the addition of a protein A layer that helped immobilized antibodies find their orientation [58]. Five DENV serotype 2 (DENV-2) positive and ten DENV serotype 1 negative sera were evaluated along with spiking samples, clinical specimens, and optimally pretreated samples. The developed immunochips could differentiate samples that were DENV-2 positive from samples that were DENV-negative [58]. The NS1 antigen ELISA had similar sensitivity. The immunosensors that are described in these two publications are distinguished by modest technical requirements for the test site, simple result interpretation and quick availability of results. Dilution or other pretreatments are frequently not necessary for the examination of samples [58]. The assay's shelf life may be increased by substituting these artificial binding sites for monoclonal antibodies, and the assay's specificity may be more precisely controlled [58]. This DNA-QCM approach is label-free and doesn't need expensive equipment, but it has similar sensitivity and specificity to fluorescent real-time PCR. Although QCM chips have been used successfully in protein tests, their usage with clinical samples may be constrained by interference from serum proteins, intricate interactions between interfacial parameters, and environmental factors [58]. Therefore, future work with this technology will focus on making more improvements that address the robustness issue.

*Nano-Technology*

Recently, progress has been made in the diagnosis of arboviruses using nanostructures, including carbon nanotubes, metal nanoparticles, liposomes, and others, for the creation of biosensors [59]. Researchers have become interested in this technology since it may allow for quick and affordable detection outside of the lab as well as increased amplification and sensitivity. Eivazzadeh-Keihan et al. (2019) states that the use of nanobiosensors enables us to considerably optimize the amount of samples used, the analysis duration, the detection limit, and the potential detection of analytes in samples unusable by conventional methods. In order to aid in the quick identification of critical mosquito-borne diseases like dengue, chikungunya, zika and yellow fever, the development of new diagnostic procedures using nanotechnology has received considerable attention [60]. To diagnose arboviruses, for instance, metallic nanoparticles linked to electrochemical biosensors have been produced [61]. Metallic nanoparticles (MNP) are tiny metal particles, such as zinc, iron, gold and silver, that are created at the nanoscale. Due to their distinctive magnetic and mechanical properties, as well as unique technological traits like melting point and surface, as well as pharmaceutical applications and biological properties of MNP, these materials have begun to stand out with the development of. MNP is therefore a promising approach for developing improved diagnostic tools and nanomedicines [61]. For instance, Simao et al (2020) showed how metallic nanoparticles connected to electrochemical biosensors could be used as arbovirus diagnostic tools. In serological samples from infected patients, the new approach demonstrated good viability and sensitivity when interacting with viral glycoproteins [62].

## Potential biomarkers for arboviral infections

Despite numerous procedures or platforms that have been developed for early detection of arboviruses, they remain suboptimal and the gold standard remain isolation and identification of viral particles but it can be time consuming, so biomarkers for diagnosis still play significant roles in arboviral infections [63, 64]. Most times disease progression is characterized by engagement of host defense pathways which include inflammation, angiogenesis, coagulation and endothelial activation [63, 64]. Biomarkers from this immunopathological pathways can be used in combination with clinical laboratory test for early detection of pathogens.

*Inflammatory Cytokines*

Most arboviral infections are immune-mediated and induces cytokine storm which contributes to the pathogenesis of the viral infections. Cytokines could be activated by virus infected cells or other cells of the immune systems such as the mast cells or T cells [65]. These cytokines play a crucial role in modulating the immune response during DENV infection [65]. A study conducted by Zhao et al. (2021) demonstrated that elevated levels of IL-6, IL-10 and TNF-α are associated with severe dengue cases, indicating their potential as predictive biomarkers for disease severity. Furthermore, a research conducted by Puc et al. (2021) highlighted the role of IL-10 in distinguishing dengue from other febrile illnesses, emphasizing its potential diagnostic

value. Notably, a comprehensive meta-analysis by Soo et al. (2017) consolidated evidence from multiple studies and supported the significance of IL-8, IL-10 and IL-18 in predicting severe dengue outcomes. A meta-analysis by Tran et al. (2021) also indicated the significance of IL-4, IL-6, IL-8, IL-10 and IL-17 in the pathogenesis of developing a severe reaction in dengue fever. Collectively, these recent studies underscore the value of inflammatory cytokines as promising biomarkers for both diagnosing dengue infection and predicting its severity, offering a more precise approach to patient management and disease surveillance.

Recent studies have shed significant light on the role of inflammatory cytokines as potential biomarkers for ZIKV infection. These studies have collectively highlighted the intricate relationship between the virus and the host immune response. A study Chang et al. (2020) found a distinct pattern of cytokine expression in response to ZIKV infection, with elevated levels of interferons (IFNs), interleukins (ILs), and tumor necrosis factor-alpha (TNF-α). This cytokine profile, particularly increased levels of IFN-β and IL-10, correlated with disease severity [71, 72]. Another study by Vinhaes et al. (2020) identified a strong correlation between IL-6 and IL-10 levels and fetal microcephaly in ZIKV-infected pregnant women, underscoring the potential of these cytokines as a predictive biomarker for adverse outcomes. Moreover, research by infection Camacho-Zavala et al. (2021) and Naveca et al. (2018) demonstrated the significance of chemokines such as CXCL10 as crucial mediators of immune responses during ZIKV infection. These chemokines were found to be upregulated in the serum of pregnant women and fetal brain cells, suggesting their role in microcephaly associated with the viral infection [76]. The high levels of these pro-inflammatory biomarkers increase the permeability of the blood-brain barrier and may facilitate the transmission of the virus from the circulation to the central nervous system during virus clearance [77]. Furthermore, a study by Zuñiga et al. (2020) focused unique immune signature of serum cytokine and chemokine dynamics in patients with ZIKV infection. They noted al pattern of cytokine expression, with acute stages infection marked by IL-9, IL-17A and CXCL10, while the recovery stages showed a shift towards elevated serum levels of CCL4 and CCL5.

In West Nile infection, Benzarti et al. (2023) in a study outlining the roles of interleukins, chemokines and Tumor Necrosis Factor Superfamily ligands in the pathogenesis of WNV infection. It was reported that WNV induces the release of at least 22 ILs in mammalian hosts, but only IL-1β, IL-6, IL-10, IL-12, IL-17A, IL-22 and IL-23 has been directly investigated in previous studies [79]. Chemokines such as CCL2, CCL7 and CXCL10 were also corelated with disease severity as a result of the expression of chemokine receptors including Ccr2, Ccr5, Ccr7, Cxcr2, Cxcr3, Cxcr4 and Cx3cr1 in WNV-infected models. Upregulation of TNF-α was have also been linked to cases of WNV infection in humans [79]. These observations demonstrate strong association with progression of the infection, suggest that monitoring the levels of these cytokines could serve as indicators of disease severity and aid in early intervention. A recent case report by Leis et al. (2020) reported the role of interferon-gamma (IFN-γ) in WNV infection. The study indicated that elevated levels of IFN-γ were present in patients with WNV infection, and its persistence was associated with prolonged disease duration due to lingering symptoms to WNV infection. This emphasizes the potential of IFN-γ as a prognostic biomarker for disease progression. Unsurprisingly elevated levels of TNFα, IL-2, IL-13 were reported along with IFN-γ, several months after onset of symptoms [80]. This evidently supports coincidental role of the inflammatory cells in the development protracted or delayed symptoms of the infection [80]. Elevated levels of cytokines such as IL-6, TNF-α, IL-8, IL-10, and IFN-γ have been correlated with disease severity, neurological complications, and disease progression. Monitoring these cytokines could potentially aid in timely diagnosis, risk assessment, and management strategies for WNV infections.

In recent studies, there is growing evidence highlighting the potential of inflammatory cytokines as valuable biomarkers for Chikungunya infection. A study conducted by Ninla-aesong et al. (2019) found that elevated levels of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, monocyte chemotactic protein-1 (MCP-1), MMP-1 and MMP-3 levels in patients with persistent arthralgia in comparison to healthy controls and a significant increase in TNF-α, MMP-1 and MMP-3 levels in patients with persistent arthralgia in comparison to patients who had fully recovered. This suggests that monitoring these cytokines could serve as an indicator of disease progression. Additionally, a study by [82] revealed that Chikungunya virus infection triggers elevated levels of IL-18 and IL-18BP levels chikungunya infection. Both IL-18 and IL-18BP was induced following CHIKV infection. IL-18BP was increased to regulate the activity of IL-18. TNF-α, MCP-1, IL-4, IL-6, and IL-10 levels have been reported to be maximal in the symptomatic phase, and these maximal levels were maintained in the recovery phase. An association between these cytokine levels and disease severity were reported in recent studies [83, 84]. Furthermore, a study by Sharma et al. (2021) demonstrated that the levels of IL-8, a chemokine involved in recruiting immune cells to the site of infection, were significantly elevated in patients with acute Chikungunya infection. This finding suggests that IL-8 could potentially serve as a diagnostic marker for early detection of the disease. Collectively, these studies underscore the potential of inflammatory cytokines as biomarkers for Chikungunya infection. Monitoring the levels of specific cytokines such as IL-6, TNF-α, IFN-γ, IL-1β, IL-18, and IL-8 could provide valuable insights into disease severity, progression, and early diagnosis. However, further research is warranted to validate the clinical utility of these cytokines as biomarkers and to establish standardized protocols for their measurement in clinical settings.

*Endothelial Activation Products*

Recent studies have shed light on the significance of endothelial activation products such as sVCAM-1, sICAM-1, and Ang-2, as potential biomarkers for early diagnosis and prognosis of arboviral infections, offering valuable insights for improving clinical management strategies.

Elevated levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble intercellular adhesion molecule-1 (sICAM-1), both endothelial activation products, have been associated with severe dengue [86–88]. Nolitriani et al. (2021) demonstrated that endothelial cell activation contributes to vascular leakage in dengue. Furthermore, a 2019 study by Mapalagamage et al. (2020) highlighted the potential of serum angiopoietin-2 (Ang-2), another marker of endothelial activation, as a predictor of severe dengue. Mariko et al. (2019) also used Angipoietin-2 levels to differentiate between dengue hemorrhagic fever patients with or without shock. Elevated von Willebrand factor levels have also been considered as a biomarker for dengue [92].

Endothelial activation is a key component of the pathogenesis of ZIKV, as the virus is known to directly infect endothelial cells [93]. A study conducted by Clé et al. (2020) found that ZIKV infection leads to an upregulation of various endothelial activation markers, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). These molecules play critical roles in leukocyte adhesion and transmigration, which are essential processes in the immune response to viral infections. Clé et al. (2020) also found out the marked increase of E-selectin in his study, which also demonstrates the potentials of E-selectin as a promising biomarker for ZIKV infection. The study carried out by Fares-Gusmao et al. (2019) also demonstrates the E-selectin as a biomarker for ZIKV infection.

WNV infection have also linked with inducement and upregulation of endothelial activation products. Roe et al. (2014) findings demonstrated a significant elevation in ICAM-1, VCAM-1, and E-selectin in human endothelial cells and infected mice brain. This suggests that endothelial activation may play a pivotal role in the pathogenesis of WNV and that these biomarkers could serve as indicators of disease severity. Similar report was also made by Constant et al. (2023) in a study observing the differential effects of Usutu and West Nile viruses on neuroinflammation, immune cell recruitment and blood–brain barrier integrity

Recent studies on endothelial activation products as biomarkers for Chikungunya infection have provided valuable insights into the pathogenesis and diagnosis of this viral disease [98]. One notable study conducted by Wauquier et al. (2011) explored the role of soluble adhesion molecules such as ICAM-1 and VCAM-1 as indicators of endothelial activation during Chikungunya infection. The research demonstrated a significant increase in serum levels of these molecules in Chikungunya-infected individuals compared to healthy controls. Similar findings was also reported by Chirathaworn et al. (2022) in the study investigating IL-1Ra and sVCAM-1 in CHIKV infection. In addition, the involvement of von Willebrand factor (vWF) in Chikungunya pathogenesis was established by Marques et al. (2017). The case report highlighted the relationship between deep venous thrombosis and CHIKV infction and reported elevated vWF levels in in the infected patient, emphasizing its potential as a biomarker for endothelial dysfunction.

*Indicators of Tissue or Organ Damage*

Elevated liver enzymes can be used as reliable indicators of liver damage in dengue patients [102]. This was observed in a retrospective study carried out by Swamy et al. (2021) correlating liver function in dengue patients with disease severity. The study observed that increased levels of serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase were associated with dengue hemorrhagic fever and severe dengue cases. Elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in another dengue study carried out by Goweda & Faisal (2020). Elevated levels of alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP) were also similarly reported in the study carried out by Sibia et al. (2023).

Additionally, cardiac biomarkers can also be reportedly utilized the diagnosis and management of dengue patients. Lee et al. (2022) and Teo et al. (2022) reported elevated levels of cardiac troponin) and brain natriuretic peptide (BNP) respectively in individuals with severe dengue, indicating myocardial and cardiac stress. Kidney injury biomarkers have also been explored in several studies on severe dengue patients, carried out by Kosaraju et al. (2023), Koshy et al. (2021), Niroshini (2020). The studies identified elevated levels of serum creatinine and urinary albumin as potential indicators of kidney damage in severe dengue cases.

Fernandez et al. (2022) shed light on the significance of microRNAs (miRNAs) as potential biomarkers. They found that certain miRNAs, such as miR-146a and miR-155, were altered in ZIKV-infected individuals. These miRNAs are known to be involved in regulating immune responses and inflammation, suggesting their utility as indicators of tissue damage. Tabari et al. (2020) also reported the dysregulation of numerous miRNAs, including miR-4792, which were dysregulated at the intracellular level during ZIKV infection. These miRNAs are also involved in oxidative stress and neurodevelopmental processes. Recently, Bhagat et al. (2021) highlighted the importance of assessing markers of neuronal injury, such as glial fibrillary acidic protein (GFAP). Elevated levels of GFAP in cerebrospinal fluid (CSF) have been associated with ZIKV-induced neurologic complications, making them promising candidates for monitoring neural tissue damage.

He et al. (2009) highlighted the importance of monitoring serum levels of neuron-specific enolase (NSE) as a potential biomarker for neurological damage in WNV patients. Elevation of NSE in patients with severe neurological symptoms, suggesting its utility in assessing brain involvement. Studies linking cardiac troponin to

WNV associated cardiac damage have also been reported. Gao et al. (2022) and Lei et al. (2022) both reported elevated cardiac troponin in their studies on rare cases of WNV associated cardiac infections, indicating the virus's impact on cardiac tissues. Additionally, investigations into liver function biomarkers in studies such as Castaldo et al. (2020), Geerling et al. (2021) and Urošević et al. (2016) revealed that serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were significantly elevated in WNV infection with hepatic involvement. These liver enzymes could serve as early indicators of hepatic damage, prompting timely interventions. Furthermore, kidney injury molecule-1 (KIM-1) has been reported to facilitates cellular uptake of WNV, and can be used to assess renal damage in WNV-infected individuals [120].

Increased concentration of creatine kinase (CK) in CHIKV-infected individuals is one of the significant biomarkers for chikungunya infection. Studies carried out by Acosta-Reyes et al. (2023), Elfert et al. (2019), and Patwardhan et al. (2021) showed that CK levels were significantly higher in patients with chikungunya virus infection, suggesting muscle damage as a consequence of the infection. The potential of microRNAs (miRNAs) as biomarkers for chikungunya-induced organ damage have also been explored [124]. Parashar et al. (2018) and Selvamani et al. (2014) revealed that specific miRNAs, such as miR-155 and miR-146a, were upregulated in chikungunya patients indicating their involvement in the regulation of immune responses and tissue damage.

## Conclusion

Arboviral infections continue to pose a significant global burden, with their impact increasing due to factors like climate change and urbanization. The development of effective diagnostics is crucial for timely detection and management of these infections. Emerging technologies, such as Lab On A Chip (LOC), Lab On A Disc (LOAD), Microfluidic Paper-Based Analytical Devices (μPADS), Lateral Flow Devices, CRISPR-CAS 12/13, Quartz crystal microbalance (QCM) and Nano-Technology, offer promising avenues for rapid and accurate diagnosis. Furthermore, identifying suitable biomarkers, including inflammatory cytokines, antibodies, endothelial activation products and indicators of tissue or organ damage, can aid in assessing disease severity and monitoring patient response to treatment. Collaborative efforts between researchers, healthcare professionals and policymakers are essential to harness the potential of these diagnostics and biomarkers, ultimately mitigating the impact of arboviral infections on public health worldwide.

## REFERENCES / ЛИТЕРАТУРА

1. Raksakoon C., Potiwat R. Current arboviral threats and their potential vectors in Thailand. *Pathogens*. 2021; 10(1): 80. https://doi.org/10.3390/pathogens10010080
2. Weaver S.C., Forrester N.L., Liu J., Vasilakis N. Population bottlenecks and founder effects: implications for mosquito-borne arboviral emergence. *Nat. Rev. Microbiol*. 2021; 19(3): 184–95. https://doi.org/10.1038/s41579-020-00482-8
3. Wang W.H., Urbina A.N., Chang M.R., Assavalapsakul W., Lu P.L., Chen Y.H., et al. Dengue hemorrhagic fever - A systemic literature review of current perspectives on pathogenesis, prevention and control. *J. Microbiol. Immunol. Infect*. 2020; 53(6): 963–78. https://doi.org/10.1016/j.jmii.2020.03.007
4. Parija S.C. Arboviruses (arthropod-borne viruses) and rodent-borne viruses. In: *Textbook of Microbiology and Immunology*. Singapore: Springer Nature Singapore; 2023: 825–46. https://doi.org/10.1007/978-981-19-3315-8_58
5. Socha W., Kwasnik M., Larska M., Rola J., Rozek W. Vector-borne viral diseases as a current threat for human and animal health-one health perspective. *J. Clin. Med*. 2022; 11(11): 3026. https://doi.org/10.3390/jcm11113026
6. Kain M.P., Skinner E.B., Athni T.S., Ramirez A.L., Mordecai E.A., van den Hurk A.F. Not all mosquitoes are created equal: A synthesis of vector competence experiments reinforces virus associations of Australian mosquitoes. *PLoS Negl. Trop. Dis*. 2022; 16(10): e0010768. https://doi.org/10.1371/journal.pntd.0010768
7. Gómez M., Martinez D., Muñoz M., Ramírez J.D. Aedes aegypti and Ae. albopictus microbiome/virome: new strategies for controlling arboviral transmission? *Parasit. Vectors*. 2022; 15(1): 287. https://doi.org/10.1186/s13071-022-05401-9
8. Brugueras S., Fernández-Martínez B., Martínez-de la Puente J., Figuerola J., Porro T.M., Rius C., et al. Environmental drivers, climate change and emergent diseases transmitted by mosquitoes and their vectors in southern Europe: A systematic review. *Environ. Res*. 2020; 191: 110038. https://doi.org/10.1016/j.envres.2020.110038
9. Hale G.L. Flaviviruses and the traveler: around the world and to your stage. a review of West Nile, yellow fever, dengue, and Zika Viruses for the practicing pathologist. *Mod. Pathol*. 2023; 36(6): 100188. https://doi.org/10.1016/j.modpat.2023.100188
10. McEntire C.R.S., Song K.W., McInnis R.P., Rhee J.Y., Young M., Williams E., et al. Neurologic manifestations of the World Health Organization's list of pandemic and epidemic diseases. *Front. Neurol*. 2021; 12: 634827. https://doi.org/10.3389/fneur.2021.634827
11. Puntasecca C.J., King C.H., LaBeaud A.D. Measuring the global burden of chikungunya and Zika viruses: A systematic review. *PLoS Negl. Trop. Dis*. 2021; 15(3): e0009055. https://doi.org/10.1371/journal.pntd.0009055
12. Loe M.W.C., Hao E., Chen M., Li C., Lee R.C.H., Zhu I.X.Y., et al. Betulinic acid exhibits antiviral effects against dengue virus infection. *Antiviral. Res*. 2020; 184: 104954. https://doi.org/10.1016/j.antiviral.2020.104954
13. Nikookar S.H., Moosazadeh M., Fazeli-Dinan M., Zaim M., Sedaghat M.M., Enayati A. Knowledge, attitude, and practice of healthcare workers regarding dengue fever in Mazandaran Province, northern Iran. *Front. Public Health*. 2023; 11: 1129056. https://doi.org/10.3389/fpubh.2023.1129056
14. Khan A.W., Noor T., Memon U.A.A., Shakil A. Carica papaya extract: a new leaf in treating dengue? *Int. J. Surg. Glob. Heal*. 2023; 6(4): e0188. https://doi.org/10.1097/gh9.0000000000000188
15. Ushijima Y., Abe H., Nguema Ondo G., Bikangui R., Massinga Loembé M., Zadeh V.R., et al. Surveillance of the major pathogenic arboviruses of public health concern in Gabon, Central Africa: increased risk of West Nile virus and dengue virus infections. *BMC Infect. Dis*. 2021; 21(1): 265. https://doi.org/10.1186/s12879-021-05960-9
16. Bhat E.A., Ali T., Sajjad N., Kumar R., Bron P. Insights into the structure, functional perspective, and pathogenesis of ZIKV: an updated review. *Biomed. Pharmacother*. 2023; 165: 115175. https://doi.org/10.1016/j.biopha.2023.115175
17. Adams L.E., Martin S.W., Lindsey N.P., Lehman J.A., Rivera A., Kolsin J., et al. Epidemiology of dengue, chikungunya, and Zika virus disease in U.S. States and territories, 2017. *Am. J. Trop. Med. Hyg*. 2019; 101(4): 884–90. https://doi.org/10.4269/ajtmh.19-0309
18. Auriti C., De Rose D.U., Santisi A., Martini L., Piersigilli F., Bersani I., et al. Pregnancy and viral infections: Mechanisms of fetal damage, diagnosis and prevention of neonatal adverse outcomes from cytomegalovirus to SARS-CoV-2 and Zika virus. *Biochim. Biophys. Acta Mol. Basis Dis*. 2021; 1867(10): 166198. https://doi.org/10.1016/j.bbadis.2021.166198
19. Leontsini E., Maloney S., Ramírez M., Mazariegos L.M., Juárez Chávez E., Kumar D., et al. Community perspectives on Zika virus disease prevention in Guatemala: A qualitative study. *Am. J. Trop. Med. Hyg*. 2020; 102(5): 971–81. https://doi.org/10.4269/ajtmh.19-0578

20. Bonifay T., Le Turnier P., Epelboin Y., Carvalho L., De Thoisy B., Djossou F., et al. Review on main arboviruses circulating on French Guiana, an ultra-peripheric European region in South America. *Viruses*. 2023; 15(6): 1268. https://doi.org/10.3390/v15061268
21. Simon F., Caumes E., Jelinek T., Lopez-Velez R., Steffen R., Chen L.H. Chikungunya: risks for travellers. *J. Travel. Med*. 2023; 30(2): taad008. https://doi.org/10.1093/jtm/taad008
22. Fehér O.E., Fehérvári P., Tolnai C.H., Forgách P., Malik P., Jerzsele Á., et al. Epidemiology and clinical manifestation of West Nile virus infections of equines in Hungary, 2007–2020. *Viruses*. 2022; 14(11): 2551. https://doi.org/10.3390/v14112551
23. Pierson T.C., Diamond M.S. The continued threat of emerging flaviviruses. *Nat. Microbiol*. 2020; 5(6): 796–812. https://doi.org/10.1038/s41564-020-0714-0
24. Klingelhöfer D., Braun M., Kramer I.M., Reuss F., Müller R., Groneberg D.A., et al. A virus becomes a global concern: research activities on West-Nile virus. *Emerg. Microbes Infect*. 2023; 12(2): 2256424. https://doi.org/10.1080/22221751.2023.2256424
25. Shartova N., Mironova V., Zelikhina S., Korennoy F., Grishchenko M. Spatial patterns of West Nile virus distribution in the Volgograd region of Russia, a territory with long-existing foci. *PLoS Negl. Trop. Dis*. 2022; 16(1): e0010145. https://doi.org/10.1371/journal.pntd.0010145
26. Mbim E.N., Edet U.O., Okoroiwu H.U., Nwaokorie F.O., Edet A.E., Owolabi A., et al. Arbovirus and its potential to lead the next global pandemic from sub-Saharan Africa: What lessons have we learned from COVID-19? *Germs*. 2022; 12(4): 538–47. https://doi.org/10.18683/germs.2022.1358
27. Castilho de Arruda L.D., Giovanetti M., Fonseca V., Zardin M.C.S.U., Lichs G.G.C., Asato S., et al. Dengue fever surveillance in Mato Grosso do Sul: Insights from genomic analysis and implications for public health strategies. *Viruses*. 2023; 15(9): 1790. https://doi.org/10.3390/v15091790
28. Wang J., Jiang C., Jin J., Huang L., Yu W., Su B., et al. Ratiometric fluorescent lateral flow immunoassay for point-of-care testing of acute myocardial infarction. *Angew. Chem. Int. Ed. Engl*. 2021; 60(23): 13042–9. https://doi.org/10.1002/anie.202103458
29. Velders A.H., Schoen C., Saggiomo V. Loop-mediated isothermal amplification (LAMP) shield for Arduino DNA detection. *BMC Res. Notes*. 2018; 11(1): 93. https://doi.org/10.1186/s13104-018-3197-9
30. Sharma S., Kabir M.A., Asghar W. Lab-on-a-chip Zika detection with reverse transcription loop-mediated isothermal amplification-based assay for point-of-care settings. *Arch. Pathol. Lab. Med*. 2020; 144(11): 1335–43. https://doi.org/10.5858/arpa.2019-0667-OA
31. Song J., Mauk M.G., Hackett B.A., Cherry S., Bau H.H., Liu C. Instrument-free point-of-care molecular detection of Zika virus. *Anal. Chem*. 2016; 88(14): 7289–94. https://doi.org/10.1021/acs.analchem.6b01632
32. Ganguli A., Ornob A., Yu H., Damhorst G.L., Chen W., Sun F., et al. Hands-free smartphone-based diagnostics for simultaneous detection of Zika, Chikungunya, and Dengue at point-of-care. *Biomed. Microdevices*. 2017; 19(4): 73. https://doi.org/10.1007/s10544-017-0209-9
33. Wang C., Liu M., Wang Z., Li S., Deng Y., He N. Point-of-care diagnostics for infectious diseases: From methods to devices. *Nano Today*. 2021; 37: 101092. https://doi.org/10.1016/j.nantod.2021.101092
34. Liu Q., Zhang X., Chen L., Yao Y., Ke S., Zhao W., et al. A sample-to-answer labdisc platform integrated novel membrane-resistance valves for detection of highly pathogenic avian influenza viruses. *Sensor. Actuat. B. Chem*. 2018; 270: 371–81. https://doi.org/10.1016/j.snb.2018.05.044
35. Strohmeier O., Keil S., Kanat B., Patel P., Niedrig M., Weidmann M., et al. Automated nucleic acid extraction from whole blood, B. subtilis, E. coli, and Rift Valley fever virus on a centrifugal microfluidic LabDisk. *RSC Adv*. 2015; 5(41): 32144–50. https://doi.org/10.1039/c5ra03399c
36. Hin S., Lopez-Jimena B., Bakheit M., Klein V., Stack S., Fall C., et al. Fully automated point-of-care differential diagnosis of acute febrile illness. *PLoS Negl. Trop. Dis*. 2021; 15(2): e0009177. https://doi.org/10.1371/journal.pntd.0009177
37. Martinez A.W., Phillips S.T., Butte M.J., Whitesides G.M. Patterned paper as a platform for inexpensive, low-volume, portable bioassays. *Angew. Chem. Int. Ed. Engl*. 2007; 46(8): 1318–20. https://doi.org/10.1002/anie.200603817
38. Theillet G., Grard G., Galla M., Maisse C., Enguehard M., Cresson M., et al. Detection of chikungunya virus-specific IgM on laser-cut paper-based device using pseudo-particles as capture antigen. *J. Med. Virol*. 2019; 91(6): 899–910. https://doi.org/10.1002/jmv.25420
39. Chowdury M.A., Khalid F. Application of microfluidic paper-based analytical device (μPAD) to detect COVID-19 in energy deprived countries. *Int. J. Energy Res*. 2021; 45(12): 18275–80. https://doi.org/10.1002/er.6958
40. Wang Z., Yu W., Xie R., Yang S., Chen A. A strip of lateral flow gene assay using gold nanoparticles for point-of-care diagnosis of African swine fever virus in limited environment. *Anal. Bioanal. Chem*. 2021; 413(18): 4665–72. https://doi.org/10.1007/s00216-021-03408-2
41. Zheng S., Yang X., Zhang B., Cheng S., Han H., Jin Q., et al. Sensitive detection of Escherichia coli O157:H7 and Salmonella typhimurium in food samples using two-channel fluorescence lateral flow assay with liquid Si@quantum dot. *Food Chem*. 2021; 363: 130400. https://doi.org/10.1016/j.foodchem.2021.130400
42. Fogaça M.B.T., Bhunia A.K., Lopes-Luz L., de Almeida E.P.R.P., Vieira J.D.G., Bührer-Sékula S. Antibody- and nucleic acid-based lateral flow immunoassay for Listeria monocytogenes detection. *Anal. Bioanal. Chem*. 2021; 413(16): 4161–80. https://doi.org/10.1007/s00216-021-03402-8
43. Salvador M., Marqués-Fernández J.L., Bunge A., Martínez-García J.C., Turcu R., Peddis D., et al. Magnetic nanoclusters increase the sensitivity of lateral flow immunoassays for protein detection: application to pneumolysin as a biomarker for Streptococcus pneumoniae. *Nanomaterials (Basel)*. 2022; 12(12): 2044. https://doi.org/10.3390/nano12122044
44. Grant B.D., Anderson C.E., Alonzo L.F., Garing S.H., Williford J.R., Baughman T.A., et al. A SARS-CoV-2 coronavirus nucleocapsid protein antigen-detecting lateral flow assay. *PLoS One*. 2021; 16(11): e0258819. https://doi.org/10.1371/journal.pone.0258819
45. Ge Y., Wu B., Qi X., Zhao K., Guo X., Zhu Y., et al. Rapid and sensitive detection of novel avian-origin influenza A (H7N9) virus by reverse transcription loop-mediated isothermal amplification combined with a lateral-flow device. *PLoS One*. 2013; 8(8): e69941. https://doi.org/10.1371/journal.pone.0069941
46. Mao L., Ying J., Selekon B., Gonofio E., Wang X., Nakoune E., et al. Development and characterization of recombinase-based isothermal amplification assays (RPA/RAA) for the rapid detection of monkeypox virus. *Viruses*. 2022; 14(10): 2112. https://doi.org/10.3390/v14102112
47. Shelite T.R., Bopp N.E., Moncayo A., Reynolds E.S., Thangamani S., Melby P.C., et al. Isothermal recombinase polymerase amplification-lateral flow point-of-care diagnostic test for Heartland virus. *Vector. Borne Zoonotic Dis*. 2021; 21(2): 110–5. https://doi.org/10.1089/vbz.2020.2670
48. Xiong D., Dai W., Gong J., Li G., Liu N., Wu W., et al. Rapid detection of SARS-CoV-2 with CRISPR-Cas12a. *PLoS Biol*. 2020; 18(12): e3000978. https://doi.org/10.1371/journal.pbio.3000978
49. Zhou W., Hu L., Ying L., Zhao Z., Chu P.K., Yu X.F. A CRISPR-Cas9-triggered strand displacement amplification method for ultrasensitive DNA detection. *Nat. Commun*. 2018; 9(1): 5012. https://doi.org/10.1038/s41467-018-07324-5
50. Chen J.S., Ma E., Harrington L.B., Da Costa M., Tian X., Palefsky J.M., et al. CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity. *Science*. 2018; 360(6387): 436–9. https://doi.org/10.1126/science.aar6245
51. Mann J.G., Pitts R.J. PrimedSherlock: a tool for rapid design of highly specific CRISPR-Cas12 crRNAs. *BMC Bioinformatics*. 2022; 23(1): 428. https://doi.org/10.1186/s12859-022-04968-5
52. Xu B., Gong P., Zhang Y., Wang Y., Tao D., Fu L., et al. A one-tube rapid visual CRISPR assay for the field detection of Japanese encephalitis virus. *Virus Res*. 2022; 319: 198869. https://doi.org/10.1016/j.virusres.2022.198869
53. Li H., Bello A., Smith G., Kielich D.M.S., Strong J.E., Pickering B.S. Degenerate sequence-based CRISPR diagnostic for Crimean-Congo hemorrhagic fever virus. *PLoS Negl. Trop. Dis*. 2022; 16(3): e0010285. https://doi.org/10.1371/journal.pntd.0010285
54. Park B.J., Yoo J.R., Heo S.T., Kim M., Lee K.H., Song Y.J. A CRISPR-Cas12a-based diagnostic method for multiple genotypes of severe

fever with thrombocytopenia syndrome virus. *PLoS Negl. Trop. Dis*. 2022; 16(8): e0010666. https://doi.org/10.1371/journal.pntd.0010666
55. Prakrankamanant P. Quartz crystal microbalance biosensors: prospects for point-of-care diagnostics. *J. Med. Assoc. Thai*. 2014; 97(Suppl. 4): S56–64.
56. Narita F., Wang Z., Kurita H., Li Z., Shi Y., Jia Y., et al. A review of piezoelectric and magnetostrictive biosensor materials for detection of COVID-19 and other viruses. *Adv. Mater*. 2021; 33(1): e2005448. https://doi.org/10.1002/adma.202005448
57. Hegde S.S., Bhat B.R. Dengue detection: Advances and challenges in diagnostic technology. *Biosens. Bioelectron. X*. 2022; 10: 100100. https://doi.org/10.1016/j.biosx.2021.100100
58. Wu T.Z., Su C.C., Chen L.K., Yang H.H., Tai D.F., Peng K.C. Piezoelectric immunochip for the detection of dengue fever in viremia phase. *Biosens. Bioelectron.* 2005; 21(5): 689–95. https://doi.org/10.1016/j.bios.2004.12.019
59. Duarte J.L., Filippo L.D.D., Araujo V.H.S., Oliveira A.E.M.F.M., de Araújo J.T.C., Silva F.B.D.R., et al. Nanotechnology as a tool for detection and treatment of arbovirus infections. *Acta Trop*. 2021; 216: 105848. https://doi.org/10.1016/j.actatropica.2021.105848
60. Eivazzadeh-Keihan R., Pashazadeh-Panahi P., Mahmoudi T., Chenab K.K., Baradaran B., Hashemzaei M., et al. Dengue virus: a review on advances in detection and trends – from conventional methods to novel biosensors. *Mikrochim. Acta*. 2019; 186(6): 329. https://doi.org/10.1007/s00604-019-3420-y
61. Khan N.T., Khan M.J. Metallic nanoparticles fabrication methods – a brief overview. *SunKrist Nanotechnol. Nanosci. J*. 2020; 2: 1–6. https://doi.org/10.46940/snnj.02.1002
62. Simão E.P., Silva D.B.S., Cordeiro M.T., Gil L.H.V., Andrade C.A.S., Oliveira M.D.L. Nanostructured impedimetric lectin-based biosensor for arboviruses detection. *Talanta*. 2020; 208: 120338. https://doi.org/10.1016/j.talanta.2019.120338
63. John D.V., Lin Y.S., Perng G.C. Biomarkers of severe dengue disease – a review. *J. Biomed. Sci*. 2015; 22: 83. https://doi.org/10.1186/s12929-015-0191-6
64. Conroy A.L., Gélvez M., Hawkes M., Rajwans N., Liles W.C., Villar-Centeno L.A., et al. Host biomarkers distinguish dengue from leptospirosis in Colombia: a case-control study. *BMC Infect. Dis*. 2014; 14: 35. https://doi.org/10.1186/1471-2334-14-35
65. Rathore A.P., Farouk F.S., St. John A.L. Risk factors and biomarkers of severe dengue. *Curr. Opin. Virol*. 2020; 43: 1–8. https://doi.org/10.1016/j.coviro.2020.06.008
66. Zhao L., Hong W., Qiu S., Wang J., Tan X., Zhang F. The relationship between level of cytokines and onset of severe dengue and their role as early warning signs. *Chinese J. Microbiol. Immunol*. 2021; (12): 778–83. https://doi.org/10.3760/cma.j.cn112309-20210421-00131
67. Puc I., Ho T.C., Yen K.L., Vats A., Tsai J.J., Chen P.L., et al. Cytokine signature of dengue patients at different severity of the disease. *Int. J. Mol. Sci*. 2021; 22(6): 2879. https://doi.org/10.3390/ijms22062879
68. Soo K.M., Khalid B., Ching S.M., Tham C.L., Basir R., Chee H.Y. Meta-analysis of biomarkers for severe dengue infections. *PeerJ*. 2017; 5: e3589. https://doi.org/10.7717/peerj.3589
69. Tran L., Radwan I., Minh L.H.N., Low S.K., Hashan M.R., Gomaa M.D., et al. Role of cytokines produced by T helper immune-modulators in dengue pathogenesis: A systematic review and meta-analysis. *Acta Trop*. 2021; 216: 105823. https://doi.org/10.1016/j.actatropica.2021.105823
70. Chang Y., Jiang Y., Li C., Wang Q., Zhang F., Qin C.F., et al. Different gene networks are disturbed by Zika virus infection in a mouse microcephaly model. *Genomics Proteomics Bioinformatics*. 2020; 18(6): 737–48. https://doi.org/10.1016/j.gpb.2019.06.004
71. da Silva M.H.M., Moises R.N.C., Alves B.E.B., Pereira H.W.B., de Paiva A.A.P., Morais I.C., et al. Innate immune response in patients with acute Zika virus infection. *Med. Microbiol. Immunol*. 2019; 208(6): 703–14. https://doi.org/10.1007/s00430-019-00588-8
72. Rabelo K., Gonçalves A.J.D.S., Souza L.J., Sales A.P., Lima S.M.B., Trindade G.F., et al. Zika virus infects human placental mast cells and the HMC-1 cell line, and triggers degranulation, cytokine release and ultrastructural changes. *Cells*. 2020; 9(4): 975. https://doi.org/10.3390/cells9040975
73. Vinhaes C.L., Arriaga M.B., de Almeida B.L., Oliveira J.V., Santos C.S., Calcagno J.I., et al. Newborns with Zika virus-associated microcephaly exhibit marked systemic inflammatory imbalance. *J. Infect. Dis*. 2020; 222(4): 670–80. https://doi.org/10.1093/infdis/jiaa197
74. Camacho-Zavala E., Santacruz-Tinoco C., Muñoz E., Chacón-Salinas R., Salazar-Sanchez M.I., Grajales C., et al. Pregnant women infected with Zika virus show higher viral load and immunoregulatory cytokines profile with CXCL10 increase. *Viruses*. 2021; 13(1): 80. https://doi.org/10.3390/v13010080
75. Naveca F.G., Pontes G.S., Chang A.Y., Silva G.A.V.D., Nascimento V.A.D., Monteiro D.C.D.S., et al. Analysis of the immunological biomarker profile during acute Zika virus infection reveals the overexpression of CXCL10, a chemokine linked to neuronal damage. *Mem. Inst. Oswaldo Cruz*. 2018; 113(6): e170542. https://doi.org/10.1590/0074-02760170542
76. Adekola H.A., Ojo D.A., Balogun S.A., Dipeolu M.A. Serum proteogenomic investigation of C-X-C motif chemokine 10 (CXCL10) and Zika virus RNA in pregnant women of Nigerian tertiary teaching hospitals; 2022. Available at: https://ssrn.com/abstract=4313703
77. Manickam C., Sugawara S., Reeves R.K. Friends or foes? The knowns and unknowns of natural killer cell biology in COVID-19 and other coronaviruses in July 2020. *PLoS Pathog*. 2020; 16(8): e1008820. https://doi.org/10.1371/journal.ppat.1008820
78. Zuñiga J., Choreño-Parra J.A., Jiménez-Alvarez L., Cruz-Lagunas A., Márquez-García J.E., Ramírez-Martínez G., et al. A unique immune signature of serum cytokine and chemokine dynamics in patients with Zika virus infection from a tropical region in Southern Mexico. *Int. J. Infect. Dis*. 2020; 94: 4–11. https://doi.org/10.1016/j.ijid.2020.02.014
79. Benzarti E., Murray K.O., Ronca S.E. Interleukins, chemokines, and tumor necrosis factor superfamily ligands in the pathogenesis of West Nile virus infection. *Viruses*. 2023; 15(3): 806. https://doi.org/10.3390/v15030806
80. Leis A.A., Grill M.F., Goodman B.P., Sadiq S.B., Sinclair D.J., Vig P.J.S., et al. Tumor necrosis factor-alpha signaling may contribute to chronic West Nile virus post-infectious proinflammatory state. *Front. Med. (Lausanne)*. 2020; 7: 164. https://doi.org/10.3389/fmed.2020.00164
81. Ninla-Aesong P., Mitarnun W., Noipha K. Proinflammatory cytokines and chemokines as biomarkers of persistent arthralgia and severe disease after Chikungunya virus infection: A 5-year follow-up study in Southern Thailand. *Viral. Immunol*. 2019; 32(10): 442–52. https://doi.org/10.1089/vim.2019.0064
82. Chirathaworn C., Rianthavorn P., Wuttirattanakowit N., Poovorawan Y. Serum IL-18 and IL-18BP levels in patients with Chikungunya virus infection. *Viral. Immunol*. 2010; 23(1): 113–7. https://doi.org/10.1089/vim.2009.0077
83. Venugopalan A., Ghorpade R.P., Chopra A. Cytokines in acute chikungunya. *PLoS One*. 2014; 9(10): e111305. https://doi.org/10.1371/journal.pone.0111305
84. Chirathaworn C., Chansaenroj J., Poovorawan Y. Cytokines and chemokines in Chikungunya virus infection: protection or induction of pathology. *Pathogens*. 2020; 9(6): 415. https://doi.org/10.3390/pathogens9060415
85. Sharma M., Chattopadhya D., Chakravarti A., Gill S., Yumnam H. Role of pro-inflammatory IL-8 and anti-inflammatory IL-10 cytokines in dengue severity. *J. Commun. Dis*. 2021; 53(2): 69–75. https://doi.org/10.24321/0019.5138.202128
86. Liao B., Tang Y., Hu F., Zhou W., Yao X., Hong W., et al. Serum levels of soluble vascular cell adhesion molecules may correlate with the severity of dengue virus-1 infection in adults. *Emerg. Microbes. Infect*. 2015; 4(4): e24. https://doi.org/10.1038/emi.2015.24
87. Tayal A., Kabra S.K., Lodha R. Management of dengue: an updated review. *Indian J. Pediatr*. 2023; 90(2): 168–77. https://doi.org/10.1007/s12098-022-04394-8
88. Sivasubramanian S., Mohandas S., Gopalan V., Vimal Raj V., Govindan K., Varadarajan P., et al. The utility of inflammatory and endothelial factors in the prognosis of severe dengue. *Immunobiology*. 2022; 227(6): 152289. https://doi.org/10.1016/j.imbio.2022.152289
89. Nolitriani N., Mariko R., Mayetti M. Soluble vascular cell adhesion molecule-1 levels and severity of dengue hemorrhagic fever in children. *Paediatr. Indones*. 2021; 61(6): 328–35. https://doi.org/10.14238/pi61.6.2021.328-35
90. Mapalagamage M., Handunnetti S.M., Wickremasinghe A.R., Premawansa G., Thillainathan S., Fernando T., et al. High levels of serum angiopoietin 2 and angiopoietin 2/1 ratio at the critical stage of dengue hemorrhagic fever in patients and association with clinical and biochemical parameters. *J. Clin. Microbiol*. 2020; 58(4): e00436–19. https://doi.org/10.1128/JCM.00436-19

91. Mariko R., Darwin E., Yanwirasti Y., Hadinegoro S.R. The difference of angiopoietin-2 levels between dengue hemorrhagic fever patients with shock and without shock. *Open Access Maced. J. Med. Sci*. 2019; 7(13): 2119–22. https://doi.org/10.3889/oamjms.2019.569
92. Ferreira A.S., Baldoni N.R., Cardoso C.S., Oliveira C.D.L. Biomarkers of severity and chronification in chikungunya fever: a systematic review and meta-analysis. *Rev. Inst. Med. Trop. Sao Paulo*. 2021; 63: e16. https://doi.org/10.1590/S1678-9946202163016
93. Kaur G., Pant P., Bhagat R., Seth P. Zika virus E protein modulates functions of human brain microvascular endothelial cells and astrocytes: implications on blood-brain barrier properties. *Front. Cell. Neurosci*. 2023; 17: 1173120. https://doi.org/10.3389/fncel.2023.1173120
94. Clé M., Desmetz C., Barthelemy J., Martin M.F., Constant O., Maarifi G., et al. Zika virus infection promotes local inflammation, cell adhesion molecule upregulation, and leukocyte recruitment at the blood-brain barrier. *mBio*. 2020; 11(4): e01183–20. https://doi.org/10.1128/mBio.01183-20
95. Fares-Gusmao R., Rocha B.C., Sippert E., Lanteri M.C., Áñez G., Rios M. Differential pattern of soluble immune markers in asymptomatic dengue, West Nile and Zika virus infections. *Sci. Rep*. 2019; 9(1): 17172. https://doi.org/10.1038/s41598-019-53645-w
96. Roe K., Orillo B., Verma S. West Nile virus-induced cell adhesion molecules on human brain microvascular endothelial cells regulate leukocyte adhesion and modulate permeability of the in vitro blood-brain barrier model. *PLoS One*. 2014; 9(7): e102598. https://doi.org/10.1371/journal.pone.0102598
97. Constant O., Maarifi G., Barthelemy J., Martin M.F., Tinto B., Savini G., et al. Differential effects of Usutu and West Nile viruses on neuroinflammation, immune cell recruitment and blood-brain barrier integrity. *Emerg. Microbes. Infect*. 2023; 12(1): 2156815. https://doi.org/10.1080/22221751.2022.2156815
98. Tanabe I.S.B., Tanabe E.L.L., Santos E.C., Martins W.V., Araújo I.M.T.C., Cavalcante M.C.A., et al. Cellular and molecular immune response to chikungunya virus infection. *Front. Cell Infect. Microbiol*. 2018; 8: 345. https://doi.org/10.3389/fcimb.2018.00345
99. Wauquier N., Becquart P., Nkoghe D., Padilla C., Ndjoyi-Mbiguino A., Leroy E.M. The acute phase of chikungunya virus infection in humans is associated with strong innate immunity and T CD8 cell activation. *J. Infect. Dis*. 2011; 204(1): 115–23. https://doi.org/10.1093/infdis/jiq006
100. Chirathaworn C., Chansaenroj J., Chaisuriyong W., Lertmaharit S., Poovorawan Y. IL-1Ra and sVCAM-1 in chikungunya virus infection. *Acta Trop*. 2022; 233: 106548. https://doi.org/10.1016/j.actatropica.2022.106548
101. Marques M.A., Adami de Sá F.P., Lupi O., Brasil P., von Ristow A. Trombose venosa profunda e vírus chicungunha. *J. Vasc. Bras*. 2017; 16(1): 60–2. https://doi.org/10.1590/1677-5449.009616 (in Portuguese)
102. Kalluru P.K.R., Mamilla M., Valisekka S.S., Mandyam S., Calderon Martinez E., Posani S., et al. Aminotransferases in relation to the severity of dengue: a systematic review. *Cureus*. 2023; 15(5): e39436. https://doi.org/10.7759/cureus.39436
103. Swamy A.M., Mahesh P.Y., Rajashekar S.T. Liver function in dengue and its correlation with disease severity: a retrospective cross-sectional observational study in a tertiary care center in Coastal India. *Pan. Afr. Med. J*. 2021; 40: 261. https://doi.org/10.11604/pamj.2021.40.261.29795
104. Goweda R., Faisal A. A study of clinical features and laboratory profile of dengue fever in outpatient setting. *Malays. J. Public Health Med*. 2020; 20(2): 94–100. https://doi.org/10.37268/mjphm/vol.20/no.2/art.422
105. Sibia R.S., Sood A., Subedi A., Sharma A., Mittal A., Singh G., et al. Elevated serum PAR-1 levels as an emerging biomarker of inflammation to predict the dengue infection severity. *J. Med. Virol*. 2023; 95(1): e28152. https://doi.org/10.1002/jmv.28152
106. Lee I.K., Chen Y.H., Huang C.H., Hsu J.C., Chang Y.C., Kuo H.J., et al. A multicenter cohort study of severe dengue and critically ill influenza patients with elevated cardiac troponin-I: Difference clinical features and high mortality. *Travel. Med. Infect. Dis*. 2022; 47: 102281. https://doi.org/10.1016/j.tmaid.2022.102281
107. Teo A., Chia P.Y., Ramireddi G.K., Khoo S.K.M., Yeo T.W. Clinical and prognostic relevance of sST2 in adults with dengue-associated cardiac impairment and severe dengue. *PLoS Negl. Trop. Dis*. 2022; 16(10): e0010864. https://doi.org/10.1371/journal.pntd.0010864
108. Koshy K.G., Suresh M.K., Suresh M.M., Koshy D.I. The incidence and clinical profile of dengue hemorrhagic fever among patients diagnosed with dengue fever in a tertiary care centre in south India. *Int. J. Res. Med. Sci*. 2021; 9(4): 1050. https://doi.org/10.18203/2320-6012.ijrms20211349
109. Niroshini N.J. *To establish urine protein creatinine ratio as a predictor of disease severity in pediatric dengue fever:* Diss. Madurai; 2020.
110. Kosaraju A., Suresh S., Elumalai R., Matcha J., Manikantan S. #5688 Clinical Profile and Outcomes of Dengue-Induced Acute Kidney Injury (Daki): a Tertiary Centre Experience From South India. *Nephrol. Dial. Transplant*. 2023; 38(Suppl. 1): gfad063c_5688. https://doi.org/10.1093/ndt/gfad063c_5688
111. Fernandez G.J., Ramírez-Mejía J.M., Urcuqui-Inchima S. Transcriptional and post-transcriptional mechanisms that regulate the genetic program in Zika virus-infected macrophages. *Int. J. Biochem. Cell Biol*. 2022; 153: 106312. https://doi.org/10.1016/j.biocel.2022.106312
112. Tabari D., Scholl C., Steffens M., Weickhardt S., Elgner F., Bender D., et al. Impact of Zika virus infection on human neural stem Cell MicroRNA signatures. *Viruses*. 2020; 12(11): 1219. https://doi.org/10.3390/v12111219
113. Bhagat R., Kaur G.., Seth P. Molecular mechanisms of zika virus pathogenesis: An update. *Indian J. Med. Res*. 2021; 154(3): 433–45. https://doi.org/10.4103/ijmr.IJMR_169_20
114. He X., Ren J., Xu F., Ferguson M.R., Li G. Localization of West Nile virus in monkey brain: double staining antigens immunohistochemically of neurons, neuroglia cells and West Nile Virus. *Int. J. Clin. Exp. Pathol*. 2009; 3(2): 156–61.
115. Gao A.R., Nichols L., Mannuru D. A rare case of West Nile virus-associated cardiomyopathy. *Cureus*. 2022; 14(8): e28473. https://doi.org/10.7759/cureus.28473
116. Lei K., Ji W., Bhaya B., Ahsan C. A rare case of cardiac recovery after acute myocarditis from West Nile virus infection: a review of the current literature. *Case Rep. Cardiol*. 2022; 2022: 8517728. https://doi.org/10.1155/2022/8517728
117. Geerling E., Stone E.T., Steffen T.L., Hassert M., Brien J.D., Pinto A.K. Obesity enhances disease severity in female mice following West Nile virus infection. *Front. Immunol*. 2021; 12: 739025. https://doi.org/10.3389/fimmu.2021.739025
118. Castaldo N., Graziano E., Peghin M., Gallo T., D'Agaro P., Sartor A., et al. Neuroinvasive West Nile infection with an unusual clinical presentation: a single-center case series. *Trop. Med. Infect. Dis*. 2020; 5(3): 138. https://doi.org/10.3390/tropicalmed5030138
119. Urošević A., Dulović O., Milošević B., Maksić N., Popović N., Milošević I., et al. The importance of haematological and biochemical findings in patients with West Nile virus neuroinvasive disease. *J. Med. Biochem*. 2016; 35(4): 451–7. https://doi.org/10.1515/jomb-2016-0022
120. Jemielity S., Wang J.J., Chan Y.K., Ahmed A.A., Li W., Monahan S., et al. TIM-family proteins promote infection of multiple enveloped viruses through virion-associated phosphatidylserine. *PLoS Pathog*. 2013; 9(3): e1003232. https://doi.org/10.1371/journal.ppat.1003232
121. Acosta-Reyes J., Rico A., Bayona-Pacheco B., Navarro-Lechuga E., Muñoz F.L., Campo A., et al. High levels of cardiovascular biomarkers in fatal Chikungunya virus infection. *Acta Trop*. 2023; 237: 106705. https://doi.org/10.1016/j.actatropica.2022.106705
122. Elfert K.A., Abdelwahed M., Chi G. Chikungunya virus infection-related rhabdomyolysis: a case report. *Cureus*. 2019; 11(2): e4036. https://doi.org/10.7759/cureus.4036
123. Patwardhan A., Nalini A., Baishya P.P., Kulanthaivelu K., Krishnareddy H., Dutta D., et al. Case report: post-chikungunya-associated myeloneuropathy. *Am. J. Trop. Med. Hyg*. 2021; 105(4): 942–5. https://doi.org/10.4269/ajtmh.20-1277
124. Roy E., Byrareddy S.N., Reid S.P. Role of microRNAs in bone pathology during chikungunya virus infection. *Viruses*. 2020; 12(11): 1207. https://doi.org/10.3390/v12111207
125. Parashar D., Paingankar M.S., More A., Patil P., Amdekar S. Altered microRNA expression signature in chikungunya-infected mammalian fibroblast cells. *Virus Genes*. 2018; 54(4): 502–13. https://doi.org/10.1007/s11262-018-1578-8
126. Selvamani S.P., Mishra R., Singh S.K. Chikungunya virus exploits miR-146a to regulate NF-κB pathway in human synovial fibroblasts. *PLoS One*. 2014; 9(8): e103624. https://doi.org/10.1371/journal.pone.0103624

**Information about the authors:**

**Hafeez A. Adekola** ✉**–** University lecturer, PhD, Medical Microbiology and Public Health, Olabisi Onabanjo University, Ago Iwoye, Nigeria. E-mail: haderinsayor@gmail.com, Adekola.hafeez@oouagoiwoye.edu.ng; https://orcid.org/0000-0003-3132-3315

**Kareem A. Wahab –** Graduate BSc (Hons) Microbiology, Olabisi Onabanjo University, Ago Iwoye, Nigeria. E-mail: wahabkareem273@gmail.com; https://orcid.org/0009-0002-9542-3817

**Omotayo E. Odunsi –** Graduate BSc (Hons) Microbiology, Olabisi Onabanjo University, Ago Iwoye, Nigeria. E-mail: odunsiomotayo17@gmail.com; https://orcid.org/0009-0001-2653-4401

**Tobiloba A. Abesin –** Graduate BSc (Hons) Microbiology, Olabisi Onabanjo University, Ago Iwoye, Nigeria. E-mail: tobilobadeboss@gmail.com; https://orcid.org/0009-0004-2676-4700

**Oluwaseun A. Oyesanya –** Graduate BSc (Hons) Microbiology, Olabisi Onabanjo University, Ago Iwoye, Nigeria. E-mail: Oluwaseunoyesanya2018@gmail.com; https://orcid.org/0009-0007-1474-9679

**Contribution:** Adekola H.A., Wahab K.A., Odunsi O.E., Abesin T.A., Oyesanya O.A. – collecting material and writing a review.

Received 26 November 2023
Accepted 20 January 2024
Published 28 February 2024

**Информация об авторах**

**Hafeez A. Adekola** ✉ – кандидат медицинских наук, лектор университета, Факультет микробиологии, Университет Олабиси Онабанджо, Аго-Ивойе, Нигерия. E-mail: haderinsayor@gmail.com, Adekola.hafeez@oouagoiwoye.edu.ng; https://orcid.org/0000-0003-3132-3315

**Kareem A. Wahab** – Выпускник бакалавриата (с отличием) по микробиологии, Факультет микробиологии, Университет Олабиси Онабанджо, Аго-Ивойе, Нигерия. E-mail: wahabkareem273@gmail.com; https://orcid.org/0009-0002-9542-3817

**Omotayo E. Odunsi** – Выпускник бакалавриата (с отличием) по микробиологии, Факультет микробиологии, Университет Олабиси Онабанджо, Аго-Ивойе, Нигерия. E-mail: odunsiomotayo17@gmail.com; https://orcid.org/0009-0001-2653-4401

**Tobiloba A. Abesin** – Выпускник бакалавриата (с отличием) по микробиологии, Факультет микробиологии, Университет Олабиси Онабанджо, Аго-Ивойе, Нигерия. E-mail: tobilobadeboss@gmail.com; https://orcid.org/0009-0004-2676-4700

**Oluwaseun A. Oyesanya** – Выпускник бакалавриата (с отличием) по микробиологии, Факультет микробиологии, Университет Олабиси Онабанджо, Аго-Ивойе, Нигерия. E-mail: Oluwaseunoyesanya2018@gmail.com; https://orcid.org/0009-0007-1474-9679

**Участие авторов:** Adekola H.A., Wahab K.A., Odunsi O.E., Abesin T.A., Oyesanya O.A. – сбор материала и написание обзора.

Поступила 26.11.2023
Принята в печать 20.01.2024
Опубликована 28.02.2024