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LETTER TO THE EDITOR

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Advancements in chikungunya virus management: FDA approval of ixchiq vaccine and global perspectives

1 | INTRODUCTION

The recent accelerated approval by the US Food and Drug Administration (FDA) of Ixchiq marks a crucial advancement in the combat against the chikungunya virus (CHIKV).[1] As an Alphavirus within the Togaviridae family, CHIKV is predominantly transmitted by female Aedes mosquitoes. *A. aegypti* historically serves as the primary vector, and *A. albopictus* has emerged as a significant secondary vector in recent outbreaks.[2] CHIKV was first identified in 1952 in the United Republic of Tanzania.[3] It has garnered priority recognition for vaccine development due to its inclusion in the Coalition for Epidemic Preparedness Innovations list of priority pathogens.[4] The virus exhibits dual transmission cycles, urban and sylvatic, with the former involving human-to-mosquito-to-human transmission. This approval underscores the urgent need for effective prevention and control strategies against CHIKV, prompting a comprehensive understanding of its characteristics, clinical manifestations, epidemiology, diagnostic methods, and available treatment modalities.

2 | CLINICAL MANIFESTATIONS

Chikungunya fever, the clinical manifestation of CHIKV infection, is characterized by acute febrile illness with severe polyarthralgia and myalgia. Notably, neonates and the elderly bear a more substantial disease burden, with neonatal cases associated with encephalitis. Mortality rates are disproportionately higher in individuals aged 65 and above, which underscores the age-dependent severity of the disease. The acute phase lasts approximately 1 week and is followed by a chronic stage marked by persistent joint pain accompanied by ophthalmic, neurological, and cardiac symptoms.[5] After the acute phase, almost 40%–59% of affected individuals show chronic symptoms, predominantly chronic chikungunya arthritis.[4] This subset of patients experiences debilitating inflammatory arthritis marked by pain and joint destruction. It commonly exhibits similarities to rheumatoid arthritis and its associated conditions.[6]

3 | EPIDEMIOLOGY

Global epidemiology studies provide a comprehensive understanding of the incidence and impact of infectious diseases worldwide. A systematic review by Bettis et al. spanning from 1999 to 2020 sheds light on the significant global burden of CHIKV. The study reveals a significant impact of CHIKV worldwide, with notable outbreaks documented in various regions. The findings indicate that CHIKV has notably affected African, Asian, American, and European continents. In Africa, 13 outbreaks were reported across 11 countries, while in Asia, 53 outbreaks occurred in 15 countries. American countries experienced 25 outbreaks across 16 nations. Notably, Europe reported five outbreaks during the same period, highlighting the global reach of CHIKV.[7] According to WHO, urban outbreaks were initially recorded in Thailand in 1967 and in India in the 1970s.[8] Notable outbreaks, such as the 2004–2007 epidemic, affected diverse regions, including the Indian Ocean, Europe, and the Americas, collectively impacting millions and causing substantial morbidity. While the majority of CHIKV-infected individuals exhibit symptoms, 3%–28% may remain asymptomatic, according to the Centers for Disease Control and Prevention (CDC).[9]

In the year 2024, as of January 31, a total of approximately 10,000 cases of Chikungunya virus disease (CHIKVD) have been documented globally, with no fatalities recorded. Eight nations across the Americas (6) and Asia (2) reported cases of CHIKVD. Predominantly, nations in South and Central America have exhibited heightened prevalence rates of CHIKVD. Specifically, Brazil accounted for the highest caseload, with 14,189 instances, followed by Paraguay (973), Bolivia (60), and Colombia (13).[10]

4 | CLINICAL DIAGNOSIS OF CHIKVD

Diagnostic techniques for CHIKV include serological tests such as TaqMan RT-qPCR and enzyme-linked immunosorbent assays (ELISA). The in-house TaqMan RT-qPCR assay has been shown to exhibit superior sensitivity compared to commercial RT-qPCR assays and is

considered the gold standard for CHIKV detection.[11] Additionally, ELISA serves as a valuable method for CHIKV detection by verifying the presence of specific antibodies, including IgM and IgG anti-chikungunya antibodies. The direct detection of the virus in blood by RT-qPCR assays is feasible during the initial infection days.[9]

5 | TREATMENT MODALITIES FOR CHIKVD

Currently, there exists no FDA-approved specific antiviral medication for CHIKV. Consequently, the treatment regimen for infected individuals relies primarily on palliative care, employing analgesics to alleviate pain and nonsteroidal anti-inflammatory drugs (NSAIDs) to mitigate arthralgia in cases of chronic infection. However, it's worth noting that a newly approved vaccine has emerged as a potential solution, which will be discussed further. Given the similarity of symptoms with dengue, caution is exercised in using aspirin or NSAIDs until a dengue diagnosis has been excluded. Persistent joint pain and common sequelae can be managed with NSAIDs, corticosteroids, and physical therapy.[12]

6 | PREVENTION FROM CHIKVD

Prevention of CHIKV infection revolves around avoiding mosquito bites and reducing mosquito breeding sites around homes, as there is no specific preventive drug currently available. Basic precautions include wearing protective clothing, using insect repellents, ensuring screened indoor spaces, and employing mosquito nets. Individuals diagnosed with CHIKV are advised to take precautions to prevent mosquito bites during the initial week of illness when the virus can be transmitted to mosquitoes and, subsequently, to other individuals. While potential vaccines are under clinical evaluation, ongoing efforts emphasize the significance of comprehensive strategies to curtail the impact of CHIKV on global health.[9]

7 | IXCHIQ (VLA1553)

Numerous vaccines reported to be under Phase I, II, and III trials are mentioned in Table 1.

Among these, Valneva's single-dose live attenuated Ixchiq vaccine was granted recent approval. Ixchiq (VLA1553), administered as a singular intramuscular injection, underwent evaluation for safety and immunogenicity in a double-blind, randomized, placebo-controlled, phase 3 trial. On-site study visits were conducted at 7 days, 28 days, 3 months, and 6 months following vaccination, during which vaccinated individuals were assessed for safety and immunogenicity.

Conducted at 43 professional vaccine trial sites in the United States of America, the phase 3 trial involved 4115 participants randomly assigned (3:1) to receive either VLA1553 or placebo. The vulnerable groups include not only young and old persons but also those with chronic medical conditions. Administration of a single intramuscular vaccination in the deltoid region occurred on Day 1 for all participants. In the investigation evaluating the immunogenicity of the vaccine within a per-protocol cohort consisting of 362 participants, stratification by age was implemented, delineating participants into two categories: those aged 18–64 and those surpassing 65 years of age. Of the total cohort, 266 individuals were assigned to receive the VLA1553 vaccine, while 96 were designated to the placebo group. Following vaccination, within the VLA1553 cohort, a remarkable 98.9% of the 266 participants demonstrated elicitation of neutralizing antibody levels against the CHIKV after 28 days. Moreover, at the 180-day mark postvaccination, a substantial proportion of participants within the VLA1553 arm, specifically 96.3% (233 out of 242), retained antibody titers surpassing the seroprotective threshold.

VLA1553 demonstrated a generally safe profile, with uniform tolerability across all age groups under study. Serious adverse events were reported in 46 (1.5%) of 3082 participants exposed to VLA1553 and eight (0.8%) of 1033 participants in the placebo arm. Two significant adverse events, namely mild myalgia, and syndrome of inappropriate antidiuretic hormone secretion, were reported with the treatment. The vaccine's most frequently reported side effects included headache, fatigue, muscle pain, joint pain, fever, and tenderness at the injection site.[13]

8 | CONCLUSION AND RECOMMENDATIONS

The recent accelerated approval of Ixchiq (VLA1553) by the US FDA stands as a significant advancement in the battle against CHIKVD. This approval comes as a result of meticulous

TABLE 1 Comparison of different chikungunya virus vaccines.

List of vaccines	Type of vaccine	NCT number	Trail	Status
VLA1553[13]	Live-attenuated vaccine	NCT04546724	Phase 3 trial	FDA approved
PXVX0317[14]	Aluminum hydroxide-adjuvanted chikungunya virus-like particle vaccine	NCT05072080	Phase 3 trial	–
MV-CHIK[15]	Live-attenuated, measles-vectored chikungunya vaccine	NCT02861586	Phase 2 trial	–
ChAdOx1[16]	Adenoviral vector vaccine	NCT03590392	Phase 1 trial	–
mRNA-1388[17]	mRNA vaccine	NCT03325075	Phase 1 trial	–
mRNA-1944[18]	mRNA vaccine	NCT03829384	Phase 1 trial	–

evaluation through a comprehensive phase 3 trial, which provided robust evidence of the vaccine's efficacy and safety. Notably, the vaccine demonstrated a high rate of seroconversion, with nearly all vaccinated individuals developing neutralizing antibodies against the CHIKV within just 28 days of vaccination. Furthermore, sustained antibody levels above the seroprotective threshold were observed in the majority of participants, even at the 6-month follow-up mark. The approval of Ixchiq offers a beacon of hope in the prevention and control of CHIKVD, a disease burdened with significant morbidity and economic impact. By providing a safe and effective means of immunization against CHIKV, the vaccine holds promise in reducing the incidence and severity of CHIKVD outbreaks, particularly in regions where the virus is endemic or where outbreaks are frequent.

In light of the compelling evidence from clinical trials, it is strongly recommended that Ixchiq (VLA1553) be promptly integrated into routine vaccination programs, particularly in areas with a high burden of CHIKVD or where there is a heightened risk of outbreaks. Public health authorities and policymakers should prioritize the incorporation of the vaccine into national immunization schedules, ensuring equitable access to all eligible populations. Furthermore, ongoing surveillance and research efforts are crucial to continuously monitor the long-term efficacy, safety, and effectiveness of Ixchiq across diverse populations. Collaboration between stakeholders, including governments, regulatory agencies, healthcare providers, and vaccine manufacturers, is essential to facilitate the successful implementation and uptake of the vaccine. By leveraging the collective efforts of the global community, including robust vaccination strategies and comprehensive public health interventions, we can strive toward the ultimate goal of mitigating the impact of CHIKVD and safeguarding the health and well-being of populations worldwide.

AUTHOR CONTRIBUTIONS

Hamza Irfan: Conceptualization; investigation; project administration; writing—original draft; writing—review and editing; resources; supervision; methodology; validation. **Aliza Ahmed**: Investigation; conceptualization; writing—original draft; writing—review and editing; methodology; resources; formal analysis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

TRANSPARENCY STATEMENT

The lead author (Hamza Irfan) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

Hamza Irfan[1]
Aliza Ahmed[2]

[1]*Department of Medicine, Shaikh Khalifa Bin Zayed Al Nahyan Medical and Dental College, Lahore, Pakistan*
[2]*Department of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan*

Correspondence
Hamza Irfan, Shaikh Khalifa Bin Zayed Al Nahyan Medical and Dental College Lahore, G855+XRM. Sheikh Zayed Medical Complex. Khayaban-e-Jamia Punjab, Block D, Muslim Town, Lahore, Pakistan.
Email: Hamy.khr.hi@gmail.com

ORCID

Hamza Irfan https://orcid.org/0000-0002-0967-7523

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