

Antigenic and genetic analysis of 2025 Chikungunya virus outbreak in China

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The 2025 Chikungunya virus (CHIKV) epidemic in China, primarily driven by the East/Central/South African (ECSA) lineage, has resulted in over 25,600 infections and one fatality, highlighting a significant public health threat. To elucidate the virological and immunological drivers of this outbreak, a comprehensive *in silico* investigation was conducted, integrating epidemiological, phylogenetic, and immunoinformatic data across 4,662 sequences. Phylogenetic analysis reveals that the outbreak likely originated from limited recent introductions, with the ECSA lineage comprising approximately 70% of the imported isolates. Temporal tracking of B-cell epitopes indicates an increase in mutation frequencies within the E1 and E2 glycoproteins since 2016. However, mapping against 38 known neutralizing monoclonal antibodies (mAbs) demonstrates that only six mutations in the 2025 E2 protein affect mAb binding sites, with just one mutation (L210Q) impacting a major epitope cluster. This indicates that the circulating variants have not yet achieved substantial B-cell immune escape. Furthermore, T-cell epitope profiling uncovers a critical population-level genetic vulnerability. While individuals with highly frequent alleles like HLA-A*02:01 are predicted to present abundant epitopes for a robust T-cell response, prevalent HLA-C alleles in the Chinese population (HLA-C*07:02 and HLA-C*01:02) present a critically low number of CHIKV epitopes. This reduced capacity for T-cell-mediated viral clearance in a substantial demographic underscores the necessity for prophylactic measures tailored to specific genetic vulnerabilities. Consequently, future vaccine development must focus on eliciting broad-spectrum neutralizing antibodies while incorporating promiscuous T-cell epitopes to protect these vulnerable populations.

Since its initial isolation in Tanzania in the 1950s, Chikungunya virus (CHIKV) has caused massive, explosive epidemics worldwide, posing a growing global health burden. In contrast to a limited 2010 outbreak,¹ the large-scale 2025 epidemic, localized primarily in Guangdong, has brought unprecedented public prominence to this vector-borne disease in China.

Driven by the East/Central/South African (ECSA) lineage (Lineage II), this outbreak began in the 28th week of 2025. The rapid transmission was marked by notable outbreaks in Foshan and Jiangmen, with the effective reproduction number (R_e) values of 8.94 and 14.28 in the 30th and 38th week, respectively (Figure 1A upper). This led to spillover cases in neighbouring regions, including other cities in Guangdong province, Guangxi province, and the Macau-Hong Kong-Taiwan region. As of 27 December, 2025, this endemic has reached its end, resulting in over 25,600 infections and one fatality (Figure 1A lower). However, the underlying virological and immunological drivers of this endemic remain poorly understood.

We conducted a comprehensive *in silico* investigation, integrating epidemiological data, viral phylogenetic, and immunoinformatic information. The analysis is based on 4,662 sequences from GISAID² (from 1952 to October 27, 2025) using nextstrain (<https://docs.nextstrain.org/en/latest/>). The transmission analysis shows that the CHIKV isolates in China have multiple imported sources including West Africa (Senegal) together with South and

South-east Asia (India, Bangladesh, Myanmar, Thailand, Malaysia, Singapore, Indonesia, and Philippines) in recent years. The major imported lineage is ECSA, contributing approximately 70% of the isolates, while the Asian lineage accounts for about 25%. Our phylogenetic analysis provides the evolutionary context for this recent outbreak (Figure 1B). The phylogenetic tree, spanning isolates from 1951 to 2025, confirms that the 2025 isolates in Guangdong belong to the ECSA lineage, mirroring the historical prevalence of this lineage in China. Together, these data (Figures 1A upper & B) suggest the 2025 outbreak originated from a single or limited number of recent introductions, rather than from diverse strains circulating endemically.

The human immune response to CHIKV is complex, involving both humoral and cellular arms. The B-cell response generates neutralizing antibodies (Abs) that primarily target the viral envelope glycoproteins E1 and E2, which are crucial for viral entry. We analysed the temporal evolution of CHIKV from 1951 to 2025. The mutation ratio plot shows the frequency of amino acid changes over time. While many regions of the genome, particularly within the viral polymerase components, remain relatively conserved due to functional constraints, distinct hotspots of mutational activity are evident. Notable increases in mutation frequency are observed after 2016. These are located in specific variable regions of nsP3, which often plays roles in host protein interaction, and crucially, within the structural envelope glycoproteins E2 and E1.

We further tracked mutation ratios in B-cell epitope regions and their correlation with 38 known neutralising monoclonal antibody (mAb) binding profiles on the E2 and E1 glycoproteins, which are the primary targets for neutralizing antibodies (Figure 1C). To understand the biological consequences of these new mutations, we cross-referenced them with an mAb binding heatmap (Figure 1C) and further mapped the key mutation sites onto the structure of the CHIKV envelope (Figure 1D). We found that only six mutations in the E2 protein of the 2025 outbreak sequences (I74T, L181M, S194G, L210Q, I211T, and A246D) are located in the binding sites of at least one mAb. Notably, only one mutation, L210Q, is shown to be in a major epitope cluster targeted by 20 out of the 38 mAbs (Figures 1C-D), while the other mutations impacted only one or two mAbs. Together, these findings indicate that the virus circulating in the 2025 outbreak is not a rapidly evolving variant, suggesting that the 2025 CHIKV variants have not yet successfully escaped B-cell antibody recognition.

To understand host-side factors contributing to the outbreak's severity, we performed an *in silico* T-cell epitope analysis by mapping predicted Human Leukocyte Antigen (HLA) Class I binding peptides across the CHIKV proteome using Fusion-pM (Figure 1E).³ This revealed epitope-dense "hotspots" in the non-structural proteins (nsP1, nsP2, nsP3 and nsP4), as well as in the structural proteins (C, E3, E2, 6K, and E1). This confirms that the virus provides ample targets for T-cell recognition, provided the host possesses the correct HLA molecules. We also correlated epitope counts with HLA allele frequencies in the Chinese population, to investigate whether the specific HLA alleles prevalent in the Chinese population were "good" or "poor" presenters of these epitopes (Figure 1E Lower). Some highly frequent

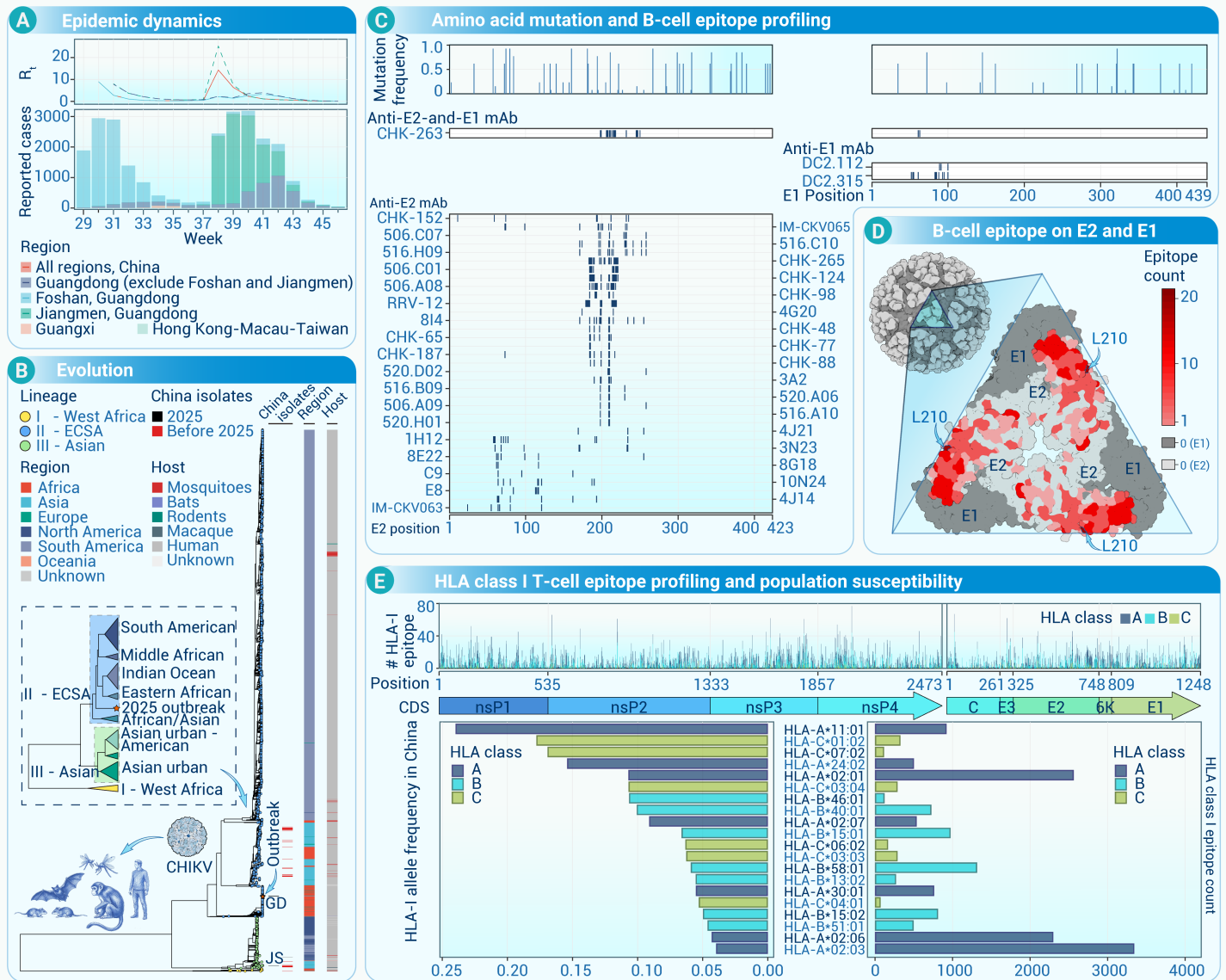


Figure 1. Antigenic and genetic analysis of 2025 Chikungunya Virus (CHIKV) outbreak in China (A) (Upper) The effective reproduction number (R_t) was calculated by the week of the year (Week 29 to 52). R_t was estimated by EpiEstim (<https://mrc-ide.github.io/EpiEstim/>) (R 4.4.2), using data from Centres for Disease Control and Prevention of China. (Lower) Epidemic statistics of the 2025 CHIKV outbreak in China over the same time period. (B) Maximum likelihood phylogenetic tree of global CHIKV strains. A magnified inset box is included to clearly display the topological relationships among key reference lineages. Major lineages, host, isolation region are color-coded. The 2025 China isolates are highlighted, representing the Guangdong (GD) outbreak and one Jiangsu (JS) imported case. (C) CHIKV-neutralizing monoclonal antibodies (mAbs) with the binding sites of these known mAbs. (D) The structure of the CHIKV E1 and E2 highlighting the B-cell epitopes and the spatial distribution of key mutation sites. The structure template was obtained from the Protein Data Bank (PDB ID: 2XFB). The position of L210 is labelled. (E) (Upper) Distribution of predicted HLA Class I binding epitopes across the CHIKV proteome. (Lower) A CHIKV susceptibility map comparing per-allele epitope presentation (right) with allele frequency in China (left) of HLA alleles with top 20 frequencies. The frequency data was obtained from Allele Frequency Net Database (<https://www.allelefrequencies.net/>).

alleles are also strong epitope presenters. For example, HLA-A*02:01 has a high frequency (over 10%) and is predicted to present the highest number of CHIKV epitopes (count > 2,500). Individuals with this allele are likely to mount a robust T-cell response. However, our T-cell analysis identified a critical population-level vulnerability: two highly prevalent HLA-C alleles in China, HLA-C*07:02 (freq. ~15%) and HLA-C*01:02 (freq. ~10%), are predicted to present a critically low number of CHIKV Class I epitopes (count < 500). This suggests a reduced capacity for T-cell-mediated viral clearance in a substantial portion of the population if they only have poorly presenting alleles. This finding suggests that a substantial fraction of the Chinese population may be genetically ill-equipped to mount an effective CD8⁺ T-cell response against CHIKV. This result parallels the vulnerability hypothesis for HLA alleles in SARS-CoV-2 infection, where poor presentation by HLA-B*46:01 was linked to disease severity, while strong presentation by HLA-B*15:01 was associated with asymptomatic infection.⁴

Our immunoinformatic findings have immediate and critical implications for vaccine development though our findings are primarily predictive due to

the current lack of *in vitro* experimental validation. Future vaccine candidates must therefore be based on current circulating strains or, more robustly, be designed to elicit antibodies against highly conserved epitopes that are not currently mutating. Furthermore, an ideal vaccine should also induce T-cell immunity, particularly for the vulnerable population carrying the HLA-C*01:02 or HLA-C*07:02 alleles. Recent research suggests that adding T-cell epitopes to a BCG vaccine exceeded BCG's protection in mouse models.⁵ Therefore, a successful next-generation CHIKV vaccine should induce broad-spectrum neutralizing antibodies and include promiscuous T-cell epitopes demonstrated to bind to a wide array of HLA supertypes.

In conclusion, the 2025 CHIKV outbreak in China highlights a growing public health crisis driven by global environmental shifts and specific genetic vulnerabilities. Our analysis provides actionable immunological insights which must inform future intervention strategies. As rising global temperatures accelerate the geographical spread and reproductive capacity of arthropod vectors, it is imperative that China and other regions with small-scale outbreaks before proactively strengthen research, policy, and monitoring for

the increased emergence of vector-borne diseases. Consequently, greater investment in both vaccine and therapeutic drug development, designed to overcome these population-specific immune gaps, is urgently needed. Finally, robust, up-to-date genetic and antigenic tracking remains the cornerstone of preparedness, ensuring that public health responses and prophylactic measures are always based on the current circulating strains.

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AUTHOR CONTRIBUTIONS

Y.-F.H., B.-Z.Z., J.-D.H., and H.C. designed the study. J.-H.M. and Y.-F.H. analysed the data. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

Y.-F. H. is the CEO of BayVax Biotech Limited.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.