

Chikungunya virus outbreak in China and treatment measures

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Abstract

Chikungunya virus (CHIKV) is a single-stranded positive-sense RNA virus in the *Togaviridae* family. In 2025, CHIKV outbreaks in China were mainly imported cases, in Guangdong, Yunnan, and Hainan provinces. The virus primarily infects macrophages, epithelial cells, and other cell types, triggering a cytokine storm that leads to excessive immune responses and subsequent tissue and organ damage. There are no effective therapeutic or prophylactic measures for CHIKV infection, and clinical management remains limited to supportive care. This study aimed to identify safe and effective pharmacological treatments to inhibit CHIKV replication and alleviate the resulting cytokine storm. After reviewing researches on the structure, life cycle of CHIKV, and efficacious compounds against RNA viruses in the past, ivermectin and vitamin D showed promising future to control CHIKV infection. Ivermectin, a broad-spectrum antiviral agent, suppresses CHIKV replication in *in vitro* models. During the coronavirus disease 2019 pandemic, ivermectin improved patient survival rates, particularly when administered in early infection. Its efficacy surpassed other anti-COVID19 drug such as azvudine, without liver injury concerns. Vitamin D exerts immunomodulatory effects by enhancing immune defense mechanisms, reducing pro-inflammatory cytokine production, and promoting macrophage autophagy; these processes facilitate the clearance of intracellular viral proteins and prevent cytokine storm onset. The combined administration of ivermectin and vitamin D achieves three key therapeutic effects: inhibition of CHIKV replication, enhancement of macrophage autophagy to eliminate intracellular viral proteins, and suppression of the pro-inflammatory cytokine storm. Both compounds are from nature with extensive clinical application and are recognized for their high safety profiles. Ivermectin and vitamin D have better efficacy than currently used anti-viral drug azvudine in COVID-19 trials with much lower costs for social health systems, therefore, holds promising potential for addressing CHIKV outbreaks and pandemics.

Keywords: Chikungunya virus, cytokine storm, ivermectin, autophagy, vitamin D

Background

Chikungunya virus (CHIKV) is a single-stranded,

positive-sense RNA virus of the genus *Alphavirus* in the family *Togaviridae*. It is a spherical, icosahedral particle with a diameter of 60–70 nm, comprising

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three structural layers: a nucleocapsid core, a host-derived lipid envelope, and embedded transmembrane glycoproteins (Figure 1) ^[1].

The viral genome is a linear RNA molecule of ~ 11.8 kb in length, which encodes two open reading frames (ORFs). The 5'-proximal ORF translates into four non-structural proteins (nsP1, nsP2, nsP3, nsP4) responsible for viral replication and transcription, while the 3'-proximal ORF is processed into three structural proteins: the capsid (C) protein that encapsidates the viral RNA to form the nucleocapsid, and two envelope glycoproteins (E1, E2) that mediate receptor binding, membrane fusion, and host cell entry (Figure 2). Additionally, the genome contains untranslated re-

gions at both 5' and 3' ends, which are critical for regulating viral RNA replication and translation ^[3].

The viral lifecycle includes membrane attachment through MXRA8/integrins, entry through clathrin-mediated endocytosis, uncoating and replication through nsP1-4, followed by structural protein translation (C, E3, E2, 6K, and E1), virion assembly in the endoplasmic reticulum and Golgi apparatus, and exocytosis (Figure 3) ^[4, 5].

Epidemiology

The CHIKV outbreak in Guangdong demonstrated ex-

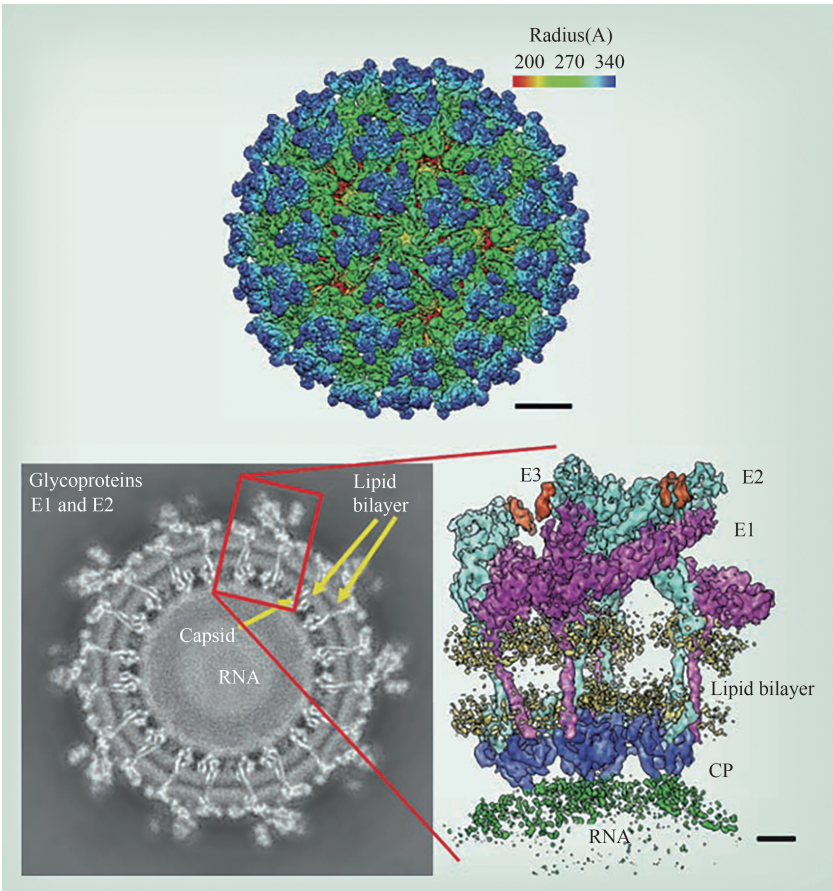


Figure 1. Cryoelectron microscopic reconstruction of the alphavirus virion structure of CHIKV ^[2].

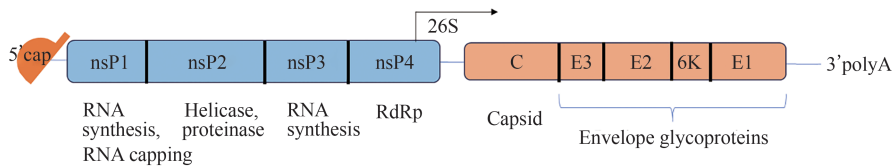


Figure 2. CHIKV genome.

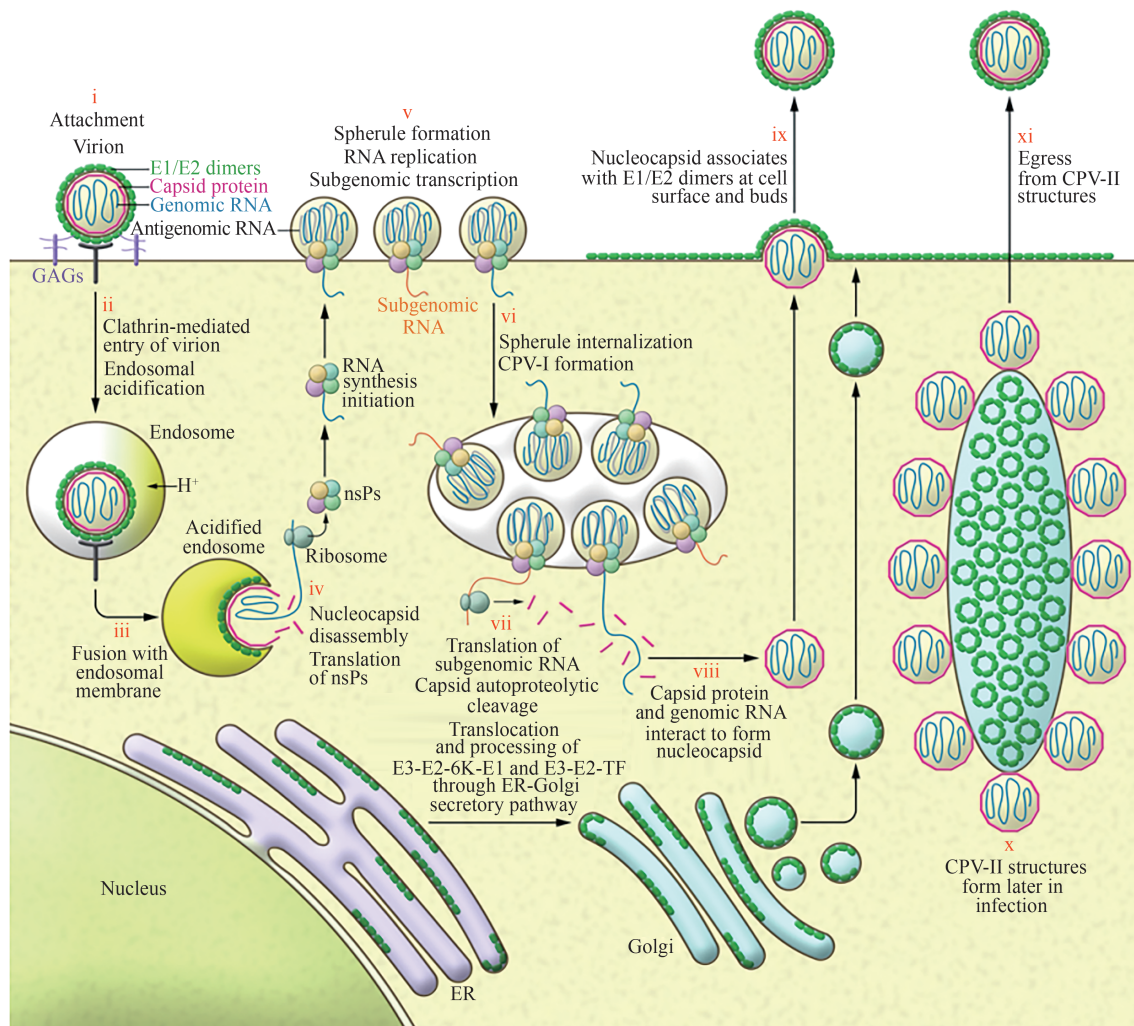


Figure 3. CHIKV replication cycle ^[4].

(i) E2 binds to the cell surface through an unknown receptor and possibly glycosaminoglycans as attachment factors. (ii) CHIKV enters the cell through clathrin-mediated endocytosis. Endosome acidification leads to E1 fusion peptide insertion into the endosomal membrane. (iii) Fusion of the viral envelope and endosomal membrane releases the nucleocapsid into the cytosol. (iv) Disassembly of the nucleocapsid liberates positive-sense genomic RNA, and nonstructural protein (nsP) translation occurs. (v) Four nsPs, together with genomic RNA and presumably host proteins, assemble at the plasma membrane (PM) and modify it to form viral replication compartments (spherules) containing viral dsRNA. nsP1–4 function as a replicase and localize to the spherule neck to generate genomic, antigenomic, and subgenomic vRNAs. (vi) Spherule internalization forms large cytopathic vacuoles (CPV-1) that house multiple spherules. Spherules at the PM or within CPV-I are fully functional. (vii) Translation of subgenomic RNA produces the structural polyprotein, and capsid autoproteolysis releases free capsid into the cytoplasm. E3-E2-6K-E1 and E2-E2-TK polyproteins translocate into the ER. E2/E1 are post-translationally modified, transit the secretory system, and are deposited at the PM. (viii) Capsid and genomic RNA interaction forms icosahedral nucleocapsids. (ix) Nucleocapsids assemble with E2/E1 at the PM, resulting in mature progeny virion budding. (x) Later in infection, CPV-IIs containing hexagonal lattices of E2/E1 form, and are studded with nucleocapsids. (xi) CPV-IIs likely serve as transport vehicles and structural protein assembly sites, allowing mature virion formation and egress.

tensive geographic dispersion across 21 cities, with a heavily concentrated epidemiological footprint (Foshan City: 10,032 cases, Jiangmen City: 5,209 cases, Guangzhou City: 590 cases, Shenzhen City: 128 cases, Zhanjiang City: 112 cases) ^[6]. Spillover trans-

mission has been documented in neighboring regions, including Guangxi Zhuang Autonomous Region (297 cases), Fujian Province (124 cases), and Hunan, Sichuan, and Hainan provinces (sporadic local cases). Genomic surveillance has revealed that the circulating

strain belongs to the East/Central/South African genotype, specifically clustering within the Central African clade (also designated as the East/Central/South African-2 sub-lineage or Middle African lineage)^[7]. Phylogenetic analysis demonstrates the highest nucleotide identity (>99%) with strains recently circulating on Réunion Island (2024-2025), suggesting direct introduction rather than long-term undetected endemic transmission (Figure 4)^[8]. According to CDC guidelines, the severe CHIKV symptoms include:

1. Acute onset fever (38–40 °C), lasting 1–7 days, often with chills, headache, myalgia, back pain, nausea, and vomiting.
2. Severe, symmetric polyarthralgia (the hallmark symptom), primarily affecting distal small joints (wrists, ankles, fingers, toes), with rapid progression (24–48 h), swelling, tenderness, and impaired mobility.
3. Maculopapular rash appearing 2–5 days post-onset, distributed on trunk, extremities, palms, and soles, often pruritic, resolving with mild desquamation.

All symptoms mentioned above are associated with cytokine storm and excessive reactive oxygen species (ROS). Therefore, taking these into consideration would help controlling CHIKV pandemic.

Current CHIKV treatment strategy

CHIKV replicates efficiently in dermal fibroblasts and skeletal muscle precursor cells at the inoculation site after entry through the MXRA8 receptor. Viral RNA replication occurs in cytoplasmic vesicles derived from endoplasmic reticulum membranes, hijacking host translational machinery. Mosquito salivary components (such as sialokinin) enhance viral replication in fibroblasts by suppressing type I interferon signaling, facilitating early systemic dissemination.

Clinical and serological evidence link CHIKV infection to a systemic inflammatory syndrome resembling MIS-C. Viral RNA is recognized by cytosolic sensors RIG-I and MDA5, triggering signaling cascades through MAVS, leading to activation of NF- κ B and IRF3/7 transcription factors (Figure 5)^[9]. Acute CHIKV infection is associated with multisystem involvement, with fever, rash, abdominal pain, vomiting, myocarditis, and coronary artery anomalies, very similar to the cases described in MIS-C related to severe acute respiratory syndrome coronavirus-2 during the coronavirus disease 2019 (COVID-19) pandemic^[10]. Overall, the cytokine storm and the following immune damage caused by CHIKV are important to treat.

The current treatment strategy for CHIKV infection is primarily supportive and symptomatic because no specific antiviral therapy or vaccine is currently available. During the acute phase (typically 3–7 days post-infection), treatment targets fever, arthralgia, and systemic inflammation. Acetaminophen (paracetamol) is the first-line agent for fever and pain relief. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, are used for arthralgia and myalgia. Corticosteroids (such as prednisone) may be considered for severe joint inflammation but must be used cautiously owing to immunosuppressive effects. Oral or intravenous fluid replacement is essential to maintain electrolyte balance, and bed rest is advised to reduce metabolic demand and prevent complications.

When the virus is released from dead cells, it is quickly recognized by the immune system. Because of the large viral load, the immune system is highly activated, releasing a large number of pro-inflammatory cytokines, tissue factors, and vasoactive peptides. These penetrate blood vessel walls and release a large amount of nitric oxide, causing secondary damage to the blood vessel wall and damaging the coagulation system. These reactions result in subsequent fever and

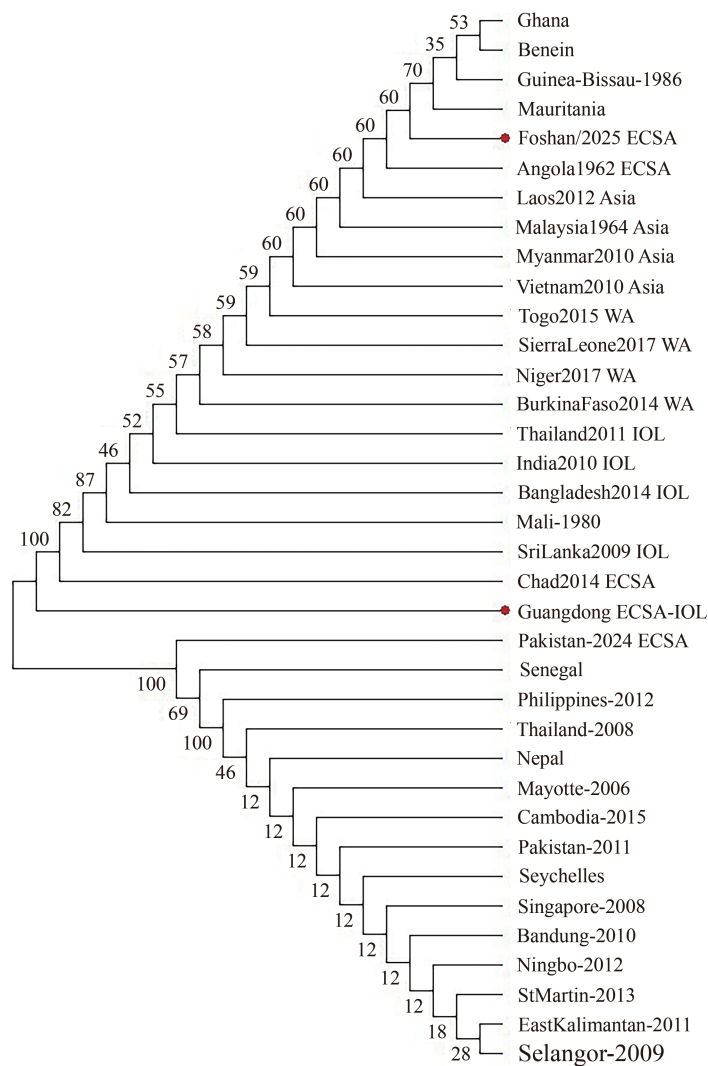


Figure 4. MCC tree of 130 CHIKV strains ^[8].

The four major lineages are highlighted with different colors representing branch evolutionary rates. The estimated 95% HPD values for most recent common ancestors are labeled beside nodes and are indicated by the thick blue horizontal node bars. Strains are labeled as follows: strain_name_location_host_date (year) of collection. The five Foshan mosquito-derived CHIKV strains are in bold. CHIKV, chikungunya virus; HPD, highest posterior density; MCC, maximum clade credibility.

internal bleeding, and can eventually lead to multiple organ failure. inflammatory damage without killing host cells.

Potential treatments

The cytokine storm poses severe risks to host homeostasis and organ integrity. This hyperinflammatory state is driven by the excessive production of pro-inflammatory mediators (including IL-6, TNF- α , MCP-1, and CXCL10), resulting in vascular leakage, tissue damage, and multi-organ dysfunction. Treatment measures should both eliminate pathogens and prevent

Ivermectin inhibits CHIKV infection in vitro

Ivermectin is a broad-spectrum anti-viral medicine. In vitro results have shown significant efficacy in preventing CHIKV infection ^[11].

To investigate its treatment potential, inhibition assays with Rluc-recombinant viruses were carried out using BHK-21 or Huh-7.5 cells. After overnight seeding in a 96-well plate at 37 °C , cells were infected with

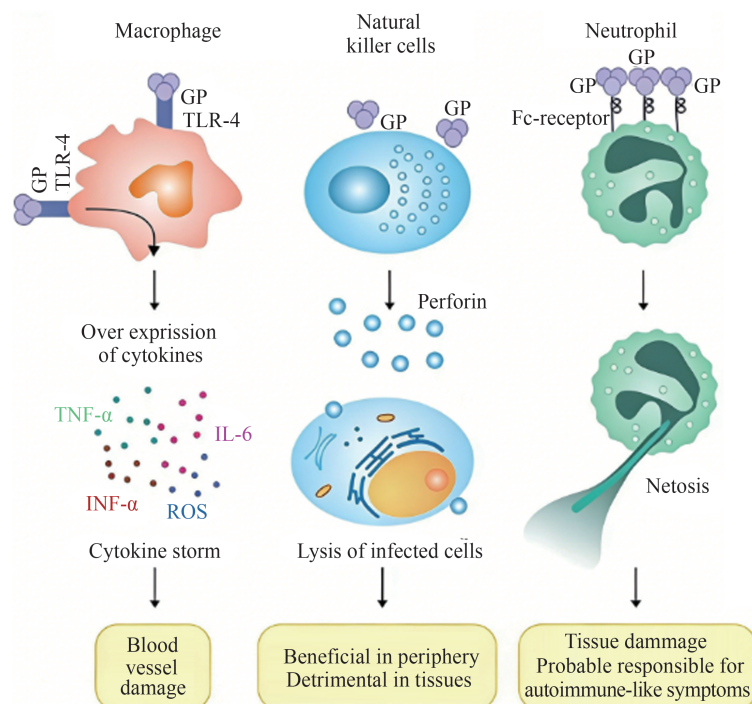


Figure 5. Cytokine storm and tissue damage.

CHIKV-Rluc at a multiplicity of infection (MOI) of 0.01 for BHK-21 cells and 0.1 for Huh-7.5 cells. The 14 investigated drugs were added after dilution in infection medium (MEM, 0.2% BSA, 20 mM HEPES, and 1 mM L-glutamine). After primary optimization, 3 μ M of investigated drugs was selected for inhibition tests. Viral replication was measured at 16 h post-infection using the Renilla Luciferase Assay System (Promega, Finnboða Varvsväg 16 pl 4131 72 NACKA, Sweden). Cell survival was measured in parallel using the CellTiter-Glo assay (Promega, Finn-

boda Varvsväg 16 pl 4131 72 NACKA, Sweden), which quantifies the amount of ATP present in metabolically active cells. Ivermectin completely abolished the luciferase signal, indicating promising protection in clinical use (Figure 6).

Next, the EC₅₀ and toxicity CC₅₀ were tested to provide the ivermectin operational window for potential clinical trials against CHIKV. Table 1 shows that the selectivity index of ivermectin was 4.1 for Huh7.5

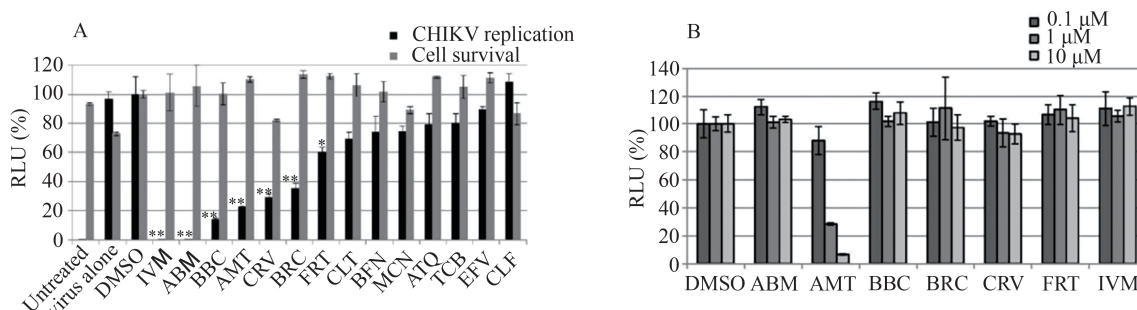


Figure 6. *In vitro* inhibition of CHIKV replication [11]. BHK-21 cells were infected with CHIKV-Rluc at MOI = 0.01, supplemented with specified compounds at 3 μ M. (A) CHIKV replication was assessed by Renilla luciferase activity in cell lysates 16 h post-infection. (B) The influence of specified compounds on RLU was assessed in parallel to remove nonspecific inhibition. Abbreviations: ABM, abamectin; IVM, ivermectin; BBC, berberine; AMT, amphotericin b; CRV, cerivastatin; BRC, bromocriptine; FRT, fenretinide; CLT, clotrimazole; BFN, bifonazole; MCN, miconazole; ATQ, atovaquone; TCB, triclabendazole; EFV, efavirenz; CLF, clofoctol.

cells and 62.4 for BHK-21 cells, indicating that it prevented CHIKV infection without harming host cells at these doses.

Ivermectin was also widely investigated by clinical technicians globally during the COVID-19 pandemic, examining prophylactic to late-phase application (Figure 7) ^[12]. Research by now shows that ivermectin treatment always lower the risks from SARS-cov-2 virus infection, which is much better than acetaminophen treatment.

Safety and clinical application of ivermectin

By now, there is no published clinical report for ivermectin against Chikungunya virus infection. However, it is widely investigated during COVID-19. Besides ivermectin, Azvudine could bind RdRp of RNA virus, therefore, interrupt the virus replication. The clinical comparison between ivermectin and azvudine is shown in Figure 8. Ivermectin achieves a 60% improvement rate across 106 studies involving 220,

000 patients, while Azvudine only shows a 27% improvement rate across 40 studies with 50,000 patients. Ivermectin reduces mortality by 47% (53 studies, 120,000 patients), whereas Azvudine's mortality reduction is 30% (29 studies, 40,000 patients). Ivermectin cuts hospitalization risk by 34% (30 studies, 120,000 patients), versus Azvudine's 10% reduction (5 studies, 4,000 patients). Ivermectin boosts recovery by 39% (40 studies, 13,000 patients), while Azvudine only improves recovery by 10% (6 studies, 5,000 patients). Ivermectin enhances viral clearance by 42% (32 studies, 4,000 patients), compared to Azvudine's 16% improvement (10 studies, 6,000 patients).

Across all measured clinical endpoints and study types, Ivermectin consistently outperforms Azvudine in improving COVID-19 outcomes, with larger effect sizes and evidence from far more studies and patients.

As for the safety, ivermectin has been massively used globally since 1987 (Mectizan from Merck), indicating a cumulative incidence of one serious adverse side

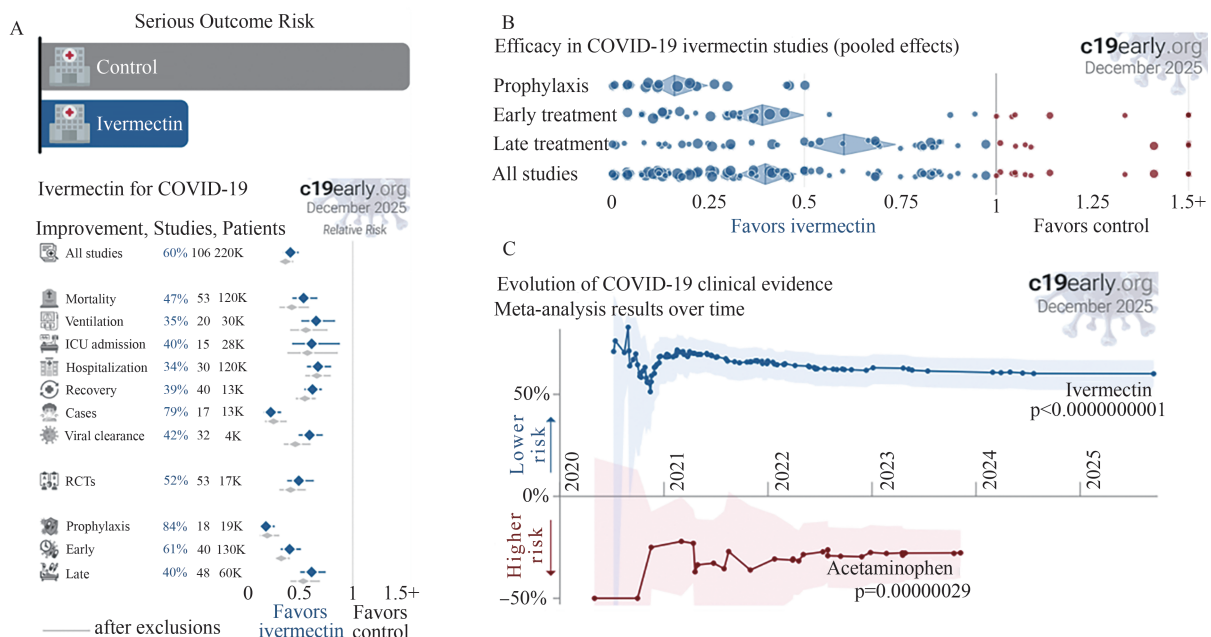


Figure 7. (A) Meta-analysis using the most serious outcome showing 61% [50%–69%] and 84% [75%–89%] lower risk for early treatment and prophylaxis, with similar results for higher quality studies, primary outcomes, peer-reviewed studies, and RCTs. (B) Individual results of ivermectin trials by treatment stage. (C) Comparison of efficacy between ivermectin and acetaminophen treatment favors ivermectin at all time points.

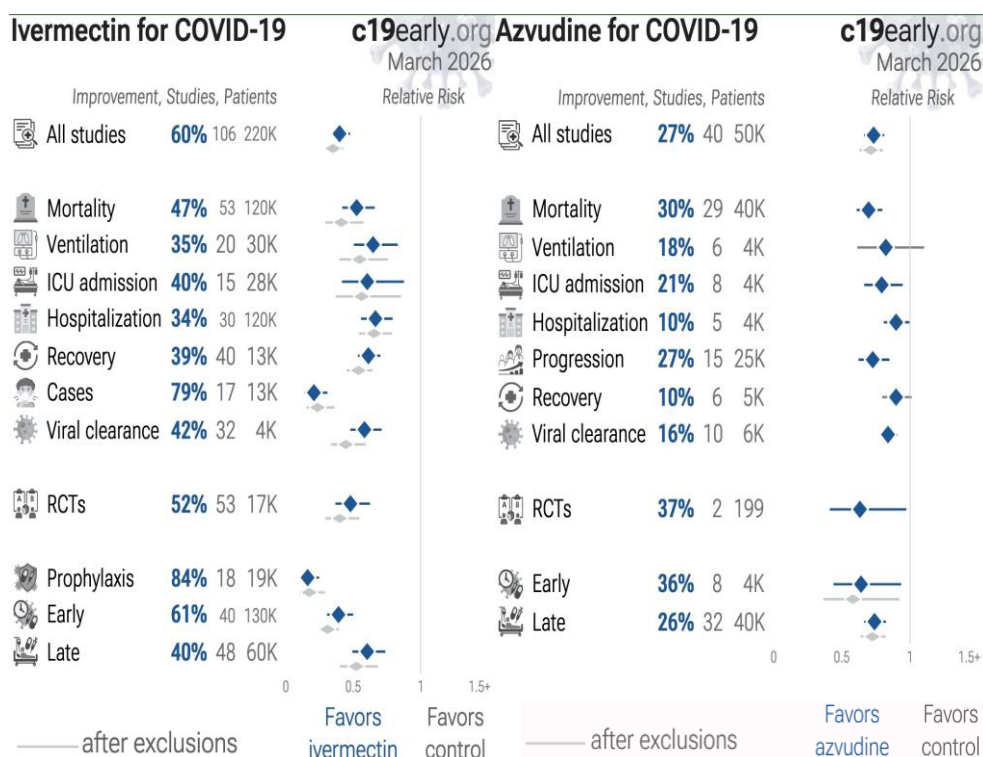


Figure 8. Clinical comparison of 106 ivermectin trials and 40 azvudine trials (c19early.org).

effect case per million ^[13]. Doses up to 2000 µg/kg are well tolerated in patients with parasitic infections ^[14]. The safety profile of ivermectin has been proven well worldwide.

Meanwhile, azvudine is a nucleoside analog with potential host cell and organ toxicity. Studies to date highlight liver, reproductive, and hematologic toxicity ^[15]. We could conclude that ivermectin is a safer choice than azvudine for longer and repeated application. As for ribavirin, it has risks of hemolytic anemia, significant teratogenicity and reproductive toxicity ^[16]. As for Glucocorticoids (GCs) and traditional immunosuppressants, when combined, lead to health risks such as weakened immune surveillance, metabolic disorders, organ toxicity, and increased susceptibility to infections, limiting their long-term clinical application ^[17]. Considering the safety and specificity, ivermectin is better than azvudine, ribavirin, GCs and traditional immunosuppressants.

In summary, ivermectin is a potential anti-CHIKV measure of clinical efficacy and no safety concern.

Vitamin D reduces CHIKV-mediated inflammatory damage

Vitamin D, primarily its biologically active form 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), has been identified by the European Food Safety Authority as having sufficient evidence for a causal relationship between intake and optimal immune system function ^[18]. Vitamin D is a steroid hormone that helps regulate the immune system by binding to specific receptors and activating genes involved in immune defense. It increases the production of antimicrobial proteins, such as cathelicidin and defensins, which fight a variety of pathogens, including bacteria, viruses, and fungi. Vitamin D supports the immune system by boosting natural defenses and promoting healthy cell connections. It helps clear respiratory pathogens through processes such as apoptosis and autophagy; it also regulates Toll-like receptors, which play a key role in immunity. Vitamin D also aids in immune cell maturation, balances inflammation, and reduces the production of proinflammatory cytokines.

Vitamin D exerts a potent regulatory role in augmenting autophagy in macrophages, a process critical for innate immunity, inflammation resolution, and intracellular pathogen clearance ^[19]. This is predominantly mediated through the vitamin D receptor signaling axis, coupled with downstream effectors including cathelecidin, mammalian target of rapamycin, beclin-1-phosphatidylinositol 3-kinase class III complex, and reactive oxygen species-mitogen-activated protein kinase pathways ^[20].

Upon binding to the vitamin D receptor, $1,25(\text{OH})_2\text{D}_3$ forms a heterodimer with the retinoid X receptor, which then binds to vitamin D response elements in the promoter regions of autophagy-associated genes. This upregulates critical autophagy initiators, including ULK1, ATG5, and ATG7, while promoting the conversion of LC3-I to LC3-II—a hallmark of autophagosome formation. Concurrently, $1,25(\text{OH})_2\text{D}_3$ suppresses mammalian target of rapamycin C1 signaling, a key negative regulator of autophagy, facilitating autophagic flux to improve macrophage intracellular pathogen clearance and modulate inflammatory responses by degrading damaged organelles and protein aggregates ^[21]. Administration of vitamin D to neonatal rats exhibiting hyperoxia-induced lung injury (as a model of bronchopulmonary dysplasia) attenuated

lung injury through various protective actions, such as preserving the integrity of lung structure, decreasing inflammation by negatively regulating Toll-like receptor 4 activation, reducing extracellular matrix deposition, and inhibiting lung cell apoptosis. Through these mechanisms, vitamin D treatment could prevent the progression of lung damage associated with airway cystic fibrosis (Figure 9).

Vitamin D has three main influences on macrophages. Vitamin D-induced autophagy is critical for macrophage clearance of intracellular pathogens such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and human immunodeficiency virus. Additionally, it alleviates tissue damage in inflammatory conditions by enhancing autophagy, including cholestatic liver injury, UV-induced skin inflammation, and sepsis-associated organ dysfunction ^[23]. Macrophage autophagy regulated by vitamin D also contributes to maintaining lipid and glucose metabolism, as well as reducing oxidative stress-related cellular damage ^[20].

Macrophages serve as reservoirs for CHIKV RNA replication; the full viral genome has been detected in joint macrophages using scRNA-seq and spatial transcriptomics ^[24]. This sustains a low-grade pro-inflammatory response (TNF, IL-1 β , and MHC-II upregula-

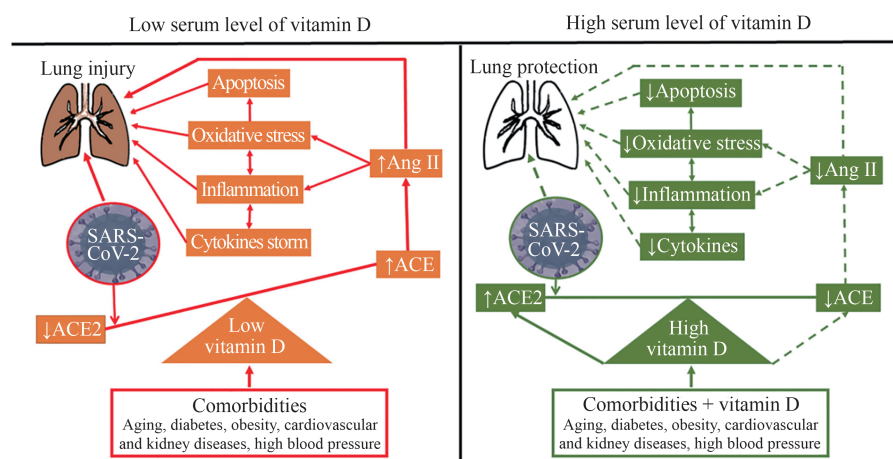


Figure 9. Graphic overview of vitamin D signaling pathways as a new potential treatment in COVID-19 lung infection ^[22].

Solid lines indicate stimulation/induction, whereas dashed lines indicate inhibition/blocking.

tion) resembling rheumatoid arthritis. Persistent viral RNA in macrophages promotes sustained CD4⁺ T cell infiltration and IFN- γ secretion, creating a positive feedback loop that maintains macrophage activation and tissue damage. Joint tissue macrophages and fibroblasts are major cellular sites of viral RNA persistence, including both positive- and negative-strand viral RNA; these macrophages are key drivers of chronic joint tissue inflammation. Treatment of mice with a small molecule inhibitor of alphavirus replication during the chronic stage not only reduced viral RNA levels in joint tissue but also mitigated the inflammatory response. Together, these findings suggest that viral RNA persistence in joint macrophages and fibroblasts is maintained by an active viral replicase, with viral RNA triggering chronic inflammation ^[21].

Autophagy activation through macrophage scavenger receptor 1 (MSR1) could restrict CHIKV infection ^[25]. Its IFN-independent antiviral function may be related to ATG5-ATG12-ATG16L1, the core components of autophagy and LAP (Figure 10). Enhancing macrophage autophagy could be beneficial during both early- and late-stage CHIKV infection.

Overall, vitamin D modulates CHIKV-mediated macrophage function primarily through reshaping pro-inflammatory cytokine secretion, tuning Toll-like receptor signaling, and regulating autophagy.

Clinical application of ivermectin and vitamin D

Ivermectin was widely investigated by clinicians globally during the COVID-19 pandemic. The dosages range from 12 to 336 mg in trials examining early treatment, late treatment, and prophylaxis (Figure 11). In a safety study, ivermectin dosages between 0.4 and 0.6 mg/kg/day were examined, with no serious adverse events reported ^[26]. In practice, dosages could range between 0.2 and 0.6 mg/kg/day.

For vitamin D, 136 treatment studies showed statistically significant lower risk for mortality, intensive care unit admission, hospitalization, and other cases. Dosages ranged from 1,800 to 400,000 IU in trials of early treatment, late treatment, and prophylaxis (Figure 12).

The mechanism of ivermectin is different from that of vitamin D, meaning they could work synergistically.

Complementary mechanisms of action

Ivermectin targets the viral replication phase, blocking viral proliferation and reducing viral load. Vitamin D targets the host inflammatory phase, inhibiting ROS accumulation and cytokine storm, thereby alleviating tissue damage. Together, they cover the entire course of CHIKV infection. It implies their potential from prophylactic to late stage application.

Reduced risks of monotherapy

High concentrations of ivermectin may carry neurotoxic risks; combination with vitamin D allows a reduction in the effective dose of ivermectin. Meanwhile, vitamin D alone exerts no direct antiviral activity, and co-administration with ivermectin compensates for this deficiency.

Improved clinical outcomes

Ivermectin controls acute viremia, while vitamin D relieves acute arthralgia and prevents chronic arthritis. Combined use shortens the disease course and ivermectin directly inhibits CHIKV replication and infection, while vitamin D facilitates innate immune system function and suppresses inflammation. Combined treatment with ivermectin and vitamin D could achieve improved efficacy by simultaneously restricting pathogens and restoring the immune system.

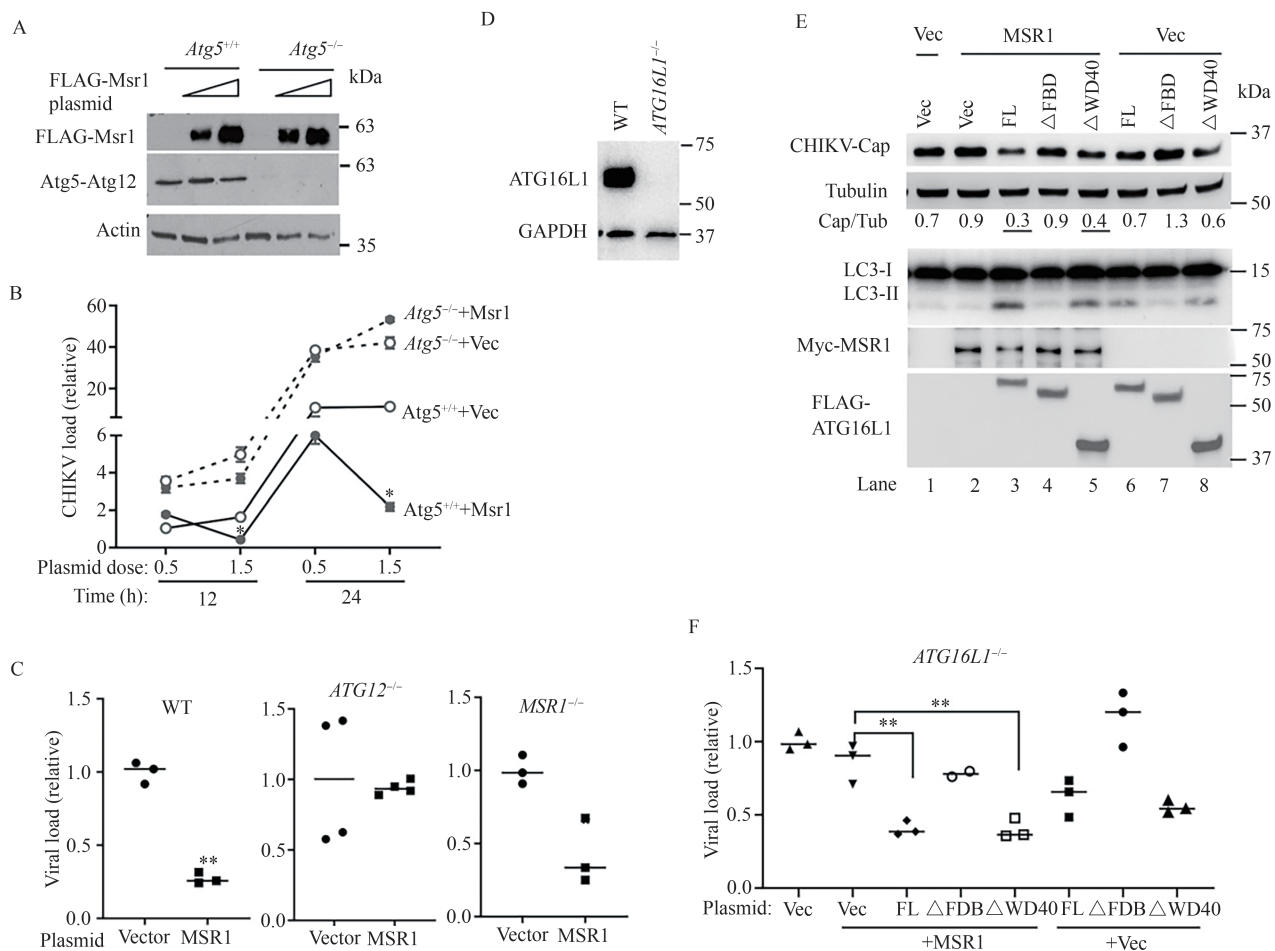


Figure 10. Inhibition of CHIKV replication by MSR1 is dependent on ATG5-ATG12-ATG16L1 ^[25]. (A, B) CHIKV replication repression by MSR1 requires ATG5. Mouse primary embryonic fibroblasts were transfected with either 0.2 or 1.5 µg of empty vector (Vec) or FLAG-Msr1 (mouse) expression plasmid. Twenty-four hours later, the cells were then infected with CHIKV (multiplicity of infection [MOI] = 0.5). (A) Immunoblots showing FLAG-Msr1 (mouse) and Atg5-Atg12 expression at 24 h after plasmid DNA transfection. (B) Quantitative RT-PCR analyses of intracellular CHIKV RNA (n = 2). (C) CHIKV replication repression by MSR1 requires ATG12. Human trophoblasts were transfected with either 0.2 µg of empty vector or a FLAG-MSR1 (human) expression plasmid. Twenty-four hours later, the cells were then infected with CHIKV (MOI = 0.5) for 12 h. Intracellular CHIKV RNA was quantified by RT-PCR (n = 3 biologically independent samples). (D) Generation of human *ATG16L1*^{-/-} trophoblasts by CRISPR-Cas9. The immunoblot shows ATG16L1 knockout efficiency. (E) CHIKV replication repression by MSR1 requires the FBD domain of ATG16L1. *ATG16L1*^{-/-} trophoblasts were transfected with the indicated combinations of expression plasmids (human gene) and vector (Vec) (50 ng each). After 24 h, the cells were infected with CHIKV (MOI = 0.5) for 16 h. FL: full-length, ΔFBD: FBD domain deletion, ΔWD40: WD40 domain deletion of ATG16L1. Immunoblots show CHIKV Capsid and cellular protein expression (n = 3 biologically independent samples). The small horizontal line indicates the median of the result. *p < 0.05, **p < 0.01 (Student's t-test).

Low cost

Ivermectin and vitamin D are patent-free. Their combined administration is low-cost, which yields substantial public health benefits for society-wide pandemic response, even though it is less attractive to capital investment.

In perspective treatment design, the low-dose group could be 20 mg ivermectin with 20,000 IU vitamin D, the mid-dose group could be 40 mg ivermectin with 40,000 IU vitamin D, and the high-dose group could be 80 mg ivermectin with 80,000 IU vitamin D. When used as treatment measures, vitamin D would help eliminating excessive ROS and cytokines, while iver-

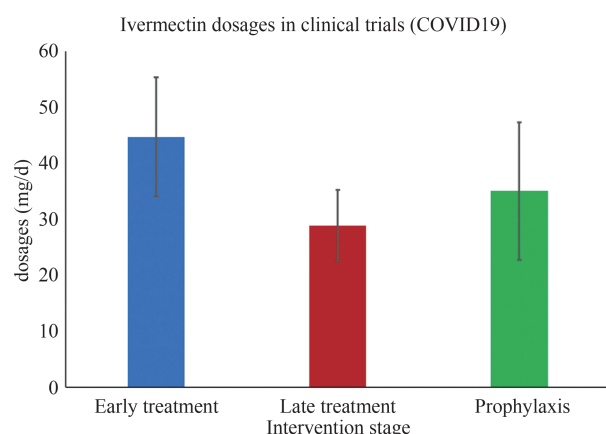


Figure 11. Dosages of ivermectin in clinical trials. Ivermectin dosages used in 106 clinical trial treatments. In a safety study, ivermectin dosages between 0.4 and 0.6 mg/kg/day were tested, with no serious adverse events reported. The average amount was near 40 mg/d.

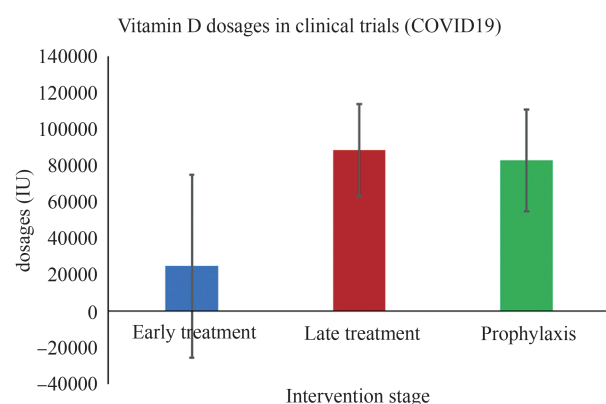


Figure 12. Dosages of vitamin D in clinical trials.

mectin would clear up pathogens. When used for prophylactic purpose, vitamin D and ivermectin are completely harmless to people. With no health concern, it is easy to convince people to join the trial. Natural products can be used for the long time of low cost.

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Conflict of interest

All authors declare no conflicts of interest.

Author contributions

Wei Miao: Conceptualization, methodology, data curation, formal analysis, visualization, and writing—original draft preparation and revision. The author read and approved the final manuscript.

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