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ADVANCES IN SOCIAL HUMANITIES RESEARCH

Knockdown Resistance (KDR) Mutations in Aedes: Global Distribution and Its Role in Vector Control Failures

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Abstract

Aedes aegypti and Aedes albopictus are major mosquito vectors of dengue, Zika, and other arboviral diseases, while pyrethroid insecticides remain widely used in vector control programs worldwide. However, repeated insecticide exposure has contributed to the selection and spread of knockdown resistance (kdr) mutations in the voltage-gated sodium channel (VGSC) gene, potentially reducing insecticide susceptibility and compromising vector control effectiveness. This literature review aimed to examine the global distribution of kdr mutations in Aedes mosquitoes, evaluate their associations with pyrethroid resistance, and discuss their implications for vector control strategies. A systematic literature search was conducted across PubMed, Scopus, ScienceDirect, and Google Scholar for studies published between 2018 and 2025. Of the 2,850 records initially identified, 14 studies met the inclusion criteria following the screening process. The findings indicated that kdr substitutions, including F1534C, V1016G, V1016I, V410L, S989P, and I1532T, were geographically widespread but unevenly distributed across regions and mosquito species. Studies from Africa reported V1016I and V410L, while investigations in Asia identified V1016G and F1534C in association with reduced pyrethroid susceptibility. Evidence from the Americas highlighted the coexistence of multiple insecticide resistance mechanisms. Combinations of kdr substitutions, particularly F1534C occurring alongside V1016G, V410L, or S989P, were associated with stronger resistance phenotypes in certain populations than individual substitutions. Metabolic resistance mechanisms frequently co-occurred with target-site resistance, and the use of the synergist piperonyl butoxide (PBO) did not consistently restore insecticide susceptibility. These findings suggested that kdr mutations represent a substantial challenge to pyrethroid-based vector control, although resistance detected through laboratory bioassays cannot be directly interpreted as evidence of operational control failure under field conditions. Integrated resistance surveillance combining molecular detection of kdr mutations, standardized phenotypic susceptibility bioassays, and assessment of metabolic resistance mechanisms is therefore essential to inform insecticide selection, improve resistance management, and sustain the effectiveness of available vector control interventions.

INTRODUCTION

Aedes mosquitoes, particularly Aedes aegypti and Aedes albopictus, are major vectors of arboviral diseases, including dengue and Zika, while Ae . aegypti is also a principal vector of yellow fever. Rapid urbanization, increased human mobility, environmental changes, and mosquito adaptability have intensified the challenges associated with vector control. Chemical insecticides remain widely used in public health programs to suppress adult mosquito populations, although their effectiveness depends on local insecticide susceptibility patterns and resistance profiles (Chaves et al., 2021; Francis et al., 2021).

Pyrethroid insecticides, including permethrin, deltamethrin, and cypermethrin, are extensively used in mosquito control because of their rapid neurotoxic effects. However, repeated exposure through public health interventions, household insecticide applications, and agricultural activities can impose substantial selection pressure on mosquito populations, favoring the survival and reproduction of resistant individuals. Consequently, resistance-associated traits may increase in frequency across successive generations. Pyrethroid resistance has been documented in Aedes populations across Asia, Africa, and the Americas, raising concerns about the sustainability of insecticide-based vector control strategies (Liu et al., 2024; Rodríguez et al., 2020; Su et al., 2019).

Insecticide resistance in mosquitoes involves several mechanisms, including target-site insensitivity, enhanced metabolic detoxification, reduced cuticular penetration, and behavioral adaptations. One of the principal target-site mechanisms is knockdown resistance (kdr), which results from specific nonsynonymous substitutions in the voltage-gated sodium channel (VGSC) gene. These substitutions can reduce the sensitivity of voltage-gated sodium channels to pyrethroids, thereby diminishing insecticide-induced neurotoxicity and increasing mosquito survival following exposure (Uemura et al., 2024).

Several kdr-associated amino acid substitutions have been identified in Aedes populations, including F1534C, V1016G, V1016I, V410L, S989P, and I1532T. Their frequencies and geographic distributions vary among mosquito populations, regions, and species. Specific combinations of these substitutions may be associated with stronger resistance phenotypes than individual substitutions, although their effects depend on genetic background and insecticide type (Silva et al., 2021). Moreover, target-site resistance frequently coexists with metabolic resistance mechanisms, particularly enhanced detoxification mediated by cytochrome P450 monooxygenases, esterases, and glutathione S-transferases. Consequently, molecular detection of kdr mutations alone cannot fully characterize the insecticide susceptibility of mosquito populations, emphasizing the need to integrate genotypic and phenotypic resistance assessments (Huang et al., 2025; Keumeni et al., 2025; Uemura et al., 2024).

Previous investigations across different geographic regions have substantially advanced understanding of the distribution and epidemiological significance of kdr mutations. In Asia, studies conducted in Indonesia, China, and Taiwan have documented the occurrence and co-occurrence of V1016G and F1534C substitutions in Ae. aegypti populations exhibiting reduced susceptibility to pyrethroid insecticides, including permethrin and deltamethrin

(Chung et al., 2022, 2025; Liu et al., 2024; Ridha et al., 2025). In Africa, investigations have reported V1016I in Benin and V410L in Burkina Faso, while studies in Cameroon have examined associations between kdr genotypes and phenotypic insecticide resistance (Keumeni et al., 2025; Lokossou et al., 2025; Toé et al., 2022). Similarly, research conducted in Mexico, Colombia, and Cuba has characterized the distribution of V410L, V1016I, and F1534C substitutions and their associations with different insecticide resistance mechanisms (Granada et al., 2021; Maestre-Serrano et al., 2023; Rodríguez et al., 2020; Solis-Santoyo et al., 2021). Collectively, these findings indicate that kdr mutations are geographically widespread, although their occurrence, frequency, and phenotypic significance differ between Ae. aegypti and Ae. albopictus populations.

Despite the growing body of evidence, several important research gaps remain. Many existing investigations have focused on individual geographic locations, mosquito populations, or specific kdr substitutions, limiting broader comparisons of mutation distribution, frequency, and co-occurrence across regions. Furthermore, although numerous studies have established associations between kdr genotypes and laboratory-measured pyrethroid resistance, evidence directly linking these mutations to operational vector control failures remains limited. Laboratory resistance phenotypes do not necessarily predict reduced intervention effectiveness under field conditions, where insecticide formulation, application practices, mosquito behavior, environmental conditions, and population characteristics may influence outcomes. The coexistence of metabolic and target-site resistance mechanisms further complicates the interpretation of molecular surveillance findings, highlighting the need for integrated assessments that distinguish genetic associations from demonstrated operational consequences.

Addressing these knowledge gaps is particularly important because the continued selection and spread of pyrethroid resistance may undermine insecticide-dependent vector control interventions. Increasing frequencies of resistance-associated alleles could reduce mosquito susceptibility to space spraying and other pyrethroid-based control measures, potentially compromising intervention effectiveness in affected areas. However, the extent to which resistance contributes to operational control failure depends on local conditions and requires direct field evaluation. Reduced insecticide effectiveness may also increase operational costs by necessitating alternative insecticides, revised application strategies, and additional surveillance activities. Therefore, synthesizing available evidence on the geographic distribution and phenotypic significance of kdr mutations is essential for supporting adaptive insecticide resistance management and optimizing the use of available vector control resources.

This review contributes to the existing literature by integrating findings from geographically diverse investigations to compare kdr mutation distributions across Aedes species and regions. Beyond identifying individual substitutions, the review examines reported associations between specific kdr genotypes, combinations of resistance-associated substitutions, and phenotypic pyrethroid resistance. It also considers the contribution of metabolic resistance mechanisms and the methodological limitations affecting comparisons

across studies. By incorporating evidence from both Ae. aegypti and Ae. albopictus, the synthesis seeks to identify species-specific and regional patterns that may be overlooked in geographically restricted or single-species investigations. This comparative approach provides a broader evidence base for interpreting molecular resistance surveillance findings and their potential implications for vector control.

The primary purpose of this literature review is to examine the global distribution of kdr mutations in Aedes mosquitoes and critically evaluate their associations with pyrethroid resistance phenotypes and potential implications for vector control effectiveness. Specifically, the review seeks to identify consistent patterns across geographic regions and mosquito species, assess evidence regarding the combined effects of resistance-associated substitutions, and examine the influence of coexisting metabolic resistance mechanisms. It also aims to identify methodological limitations and evidence gaps that constrain the interpretation of molecular resistance data, particularly regarding their relationship with operational vector control outcomes.

The findings of this review are expected to support evidence-based insecticide resistance surveillance and management. For public health authorities and vector control program managers, the synthesis provides a comparative overview of geographically relevant kdr substitutions and their reported associations with pyrethroid resistance, which may help prioritize molecular surveillance alongside standardized phenotypic susceptibility testing. For researchers, the identification of methodological inconsistencies and unresolved questions may guide future investigations into mutation interactions, fitness costs, resistance mechanisms, and the relationship between laboratory resistance and field intervention effectiveness. Integrating these findings may strengthen the interpretation of resistance surveillance data and inform more targeted insecticide resistance management strategies.

Accordingly, this study aimed to systematically review publications from 2018 to 2025 reporting kdr mutations in Aedes mosquito populations and compare their distribution across geographic regions, mosquito species, and associated pyrethroid resistance phenotypes. The review specifically examined the occurrence and co-occurrence of resistance-associated substitutions, evaluated evidence concerning their relationships with phenotypic resistance, and considered the contribution of metabolic mechanisms to observed resistance patterns. By integrating molecular and phenotypic evidence, the study sought to clarify the potential implications of kdr mutations for pyrethroid-based vector control while distinguishing laboratory-detected resistance from confirmed operational control failure. Ultimately, this synthesis aimed to support integrated resistance surveillance, guide insecticide selection, and contribute to the long-term effectiveness of vector control interventions against arboviral diseases.

METHOD

This study employed a literature review design based on published research without collecting mosquito specimens or conducting additional laboratory experiments. Literature searches were performed in PubMed, Scopus, ScienceDirect, and Google Scholar, covering

publications from 2018 to 2025. The search terms included Aedes, knockdown resistance (kdr), pyrethroid resistance, voltage-gated sodium channel (VGSC), F1534C, V1016I, V410L, S989P, and vector control.

Studies were included if they (1) were original research articles or scientific reviews with accessible full texts; (2) examined Aedes mosquitoes and insecticide resistance relevant to vector control; (3) reported findings on kdr/VGSC mutations, insecticide susceptibility bioassays, synergist assays, or implications for field-based vector control; and (4) were published in identifiable scientific journals. Publications unrelated to Aedes, focused exclusively on clinical aspects without relevance to vector control, or lacking sufficient information on insecticide resistance mechanisms were excluded.

The initial database searches identified 2,850 records, of which 236 were considered potentially relevant following title and abstract screening. After applying the eligibility criteria, 14 publications were included in the final synthesis. The selected studies were analyzed thematically according to their methodological characteristics, geographic distribution of kdr mutations, associations between multiple mutations and resistance phenotypes, contributions of metabolic resistance mechanisms, and implications for vector control programs. A detailed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was not presented because complete records of duplicate removal and stage-specific exclusion reasons were unavailable.

RESULTS AND DISCUSSION

Characteristics of Synthesized Literature

A total of 14 publications from the period 2018–2025 form the main basis for the study. These sources include resistance phenotype studies, identification of VGSC mutations, synergy response testing, and reviews of vector control strategies. The diversity of designs and species studied needs to be considered when comparing findings; not all articles measure allele frequency, mortality, and control success in the field with the same parameters. Table 1 summarizes the focus and contribution of each source to synthesis.

Table 1. Summary of the 14 publications analyzed in the literature review.

Author (year)	Focus of the article	Contributions to the study
Al Nazawi and Weetman (2023)	Aedes aegypti*'s susceptibility* to single/repeated deltamethrin exposure	Indicates that age and exposure patterns may affect the interpretation of the susceptibility test.
Chaves et al. (2021)	Observation of *Aedes* aegypti eggs, environmental factors, and arboviral cases	Provide context for vector monitoring; not direct evidence of KDR mutations.
Francis et al. (2021)	Challenges of vector infectious disease control in the Caribbean	Support the need for an integrated control strategy.
Helvecio et al. (2020)	GSTE2 polymorphism and temefos resistance in *Aedes* aegypti	Evidence of detoxification mechanisms; cannot be directly equated with pyrethroid resistance.

Author (year)	Focus of the article	Contributions to the study
Huang et al. (2025)	Mechanism of pyrethroid resistance in Culicidae in Hainan, China	Bioassay contexts, synergistic PBOs, and metabolic resistance; taxon coverage is broader than *that of Aedes*.
Keumeni et al. (2025)	KDR mutations and pyrethroid *resistance of Aedes* aegypti in Cameroon	The main evidence is the link between VGSC variants and resistance, including multilocus genotypes.
Liu et al. (2024)	Bioassay and mutation of the Aedes albopictus RDD in Zhejiang, China	Attributing KDR variation to LC50 as well as decreased insecticide susceptibility.
Lokossou et al. (2025)	Reports of V1016I mutation in *Aedes* aegypti in the port of Cotonou, Benin	Describing the emergence of the KDR variant and the importance of monitoring at the mobility gate.
Rodríguez et al. (2020)	Resistance to various insecticides in *Aedes* aegypti in Cuba	Supports the role of various resistance mechanisms in a single population.
Soni et al. (2018)	Detection of dengue vector resistance through bioassay and molecular examination	Supports phenotypic and genetic testing approaches together.
Su et al. (2019)	Development of Aedes *albopictus* insecticide resistance in Guangzhou	Describe the dynamics of rapid resistance in an urban context.
Toé et al. (2022)	V410L mutation and *multiple resistance of Aedes* aegypti in Burkina Faso	Expanding the evidence of the existence of RDC in Africa.
Uemura et al. (2024)	Review of the development of the KDR mutation study in *Aedes mosquitoes*	The basis of the interpretation of the VGSC locus and the diversity of mutation variants.
Zhou et al. (2022)	Resistance to pyrethroids combined with PBO	Support caution over PBO's synergistic ability to overcome resistance.

Global Distribution and Distribution Pattern of KDR Mutations in Aedes

The literature shows that the pattern of KDR mutations varies by geographic region and mosquito species. F1534C, V1016G, V1016I, V410L, S989P, and I1532T are the variants discussed in the study sources. Loci differences in VGSC are important because the combination of amino acid changes in multiple positions can be associated with reduced sensitivity to pyrethroids. However, the findings of one population cannot simply be generalized to the entire Aedes population (Uemura et al., 2024).

In Africa, Keumeni et al. (2025) reported the association of KDR mutations with pyrethroid resistance in Aedes aegypti in Cameroon, while Toé et al. (2022) documented V410L in the context of resistance to several insecticides in Aedes aegypti in Burkina Faso. Lokossou et al. (2025) reported the V1016I variant in Aedes aegypti in the port area of Cotonou, Benin. Together, the findings demonstrate the need for monitoring VGSC mutations in populations from diverse locations, particularly areas with high human and goods mobility.

In Asia, Liu et al. (2024) linked the findings of KDR mutations in Aedes albopictus in

Zhejiang to insecticide susceptibility parameters, including LC50. Su et al. (2019) also reported the development of resistance in Aedes albopictus in Guangzhou. The study confirms that the resistance data of Aedes albopictus need to be clearly separated from the data of Aedes aegypti. Meanwhile, reports of multiple resistance of Aedes aegypti in Cuba provide context in the Americas regarding the existence of more than one resistance mechanism (Rodríguez et al., 2020).

Table 2. Mapping of regional findings from selected literature; not global prevalence estimates.

Region/source	Species and focus	The Significance of the Findings
Africa: Cameroon	*Aedes* aegypti; KDR and pyrethroid mutations	Association of genotypes with resistance; Keumeni et al. (2025)
Africa: Burkina Faso	*Aedes* aegypti; V410L	Evidence of KDR mutations in multiple resistance; Toé et al. (2022)
Africa: Benin	*Aedes* aegypti; V1016I	Reporting of variants in the port of Cotonou; Lokossou et al. (2025)
Asia: Zhejiang	*Aedes* albopictus; variations of KDR and LC50	Phenotype linkages and molecular markers; Liu et al. (2024)
Asia: Guangzhou	*Aedes* albopictus; insecticide resistance status	Dynamics of urban resistance; Su et al. (2019)
America: Cuba	*Aedes* aegypti; resistance to various insecticides	Mutually contributing mechanisms; Rodríguez et al. (2020)

The Role of Multilocus Mutations in Increased Pyrethroid Resistance

Changes in a single position of the VGSC can affect the mosquito's response to pyrethroids, but mutations that appear at multiple loci have the potential to form a more resistant phenotype. The literature analyzed highlights F1534C alongside the V1016G, V410L, or S989P variants as combinations that need to be observed in molecular examination. Such associations should be assessed by species, genotype arrangement, as well as insecticides used in the test, rather than simply the presence of a single mutation (Keumeni et al., 2025; Uemura et al., 2024).

The study by Liu et al. (2024) on Aedes albopictus shows the importance of reading molecular data alongside phenotypic indicators such as LC50 and mortality after insecticide exposure. Conceptually, the increase in LC50 reflects the need for higher insecticide concentrations to result in the mortality of 50% of the test population. However, laboratory results cannot automatically be interpreted as a decrease in fogging results in the field without operational evaluation at the relevant site.

KDR mutation detection provides information about potential mechanisms at target sites, while bioassays assess the mosquito's live or dead response to insecticide exposure. The two complement each other in monitoring, as does the phenotypic and molecular testing approaches

discussed by Soni et al. (2018). Programs that only observe mosquito density without checking their resistance status can potentially miss changes in susceptibility before the intervention is adjusted.

Interaction of Metabolic Resistance and Piperonyl Butoxide

In addition to mutations in VGSC, insecticide resistance can be affected by increased activity of detoxifying enzymes. Piperonyl butoxide (PBO) is a synergistic compound used to inhibit a number of cytochrome P450 enzymes. Increased mortality after PBO use may be indicative of the contribution of metabolic pathways, but does not by itself identify all mechanisms at work. The literature analyzed shows that in some populations, the use of PBO does not fully restore susceptibility to pyrethroids (Huang et al., 2025; Zhou et al., 2022).

Helvecio et al. (2020) reported the association of GSTE2 polymorphism with temefos resistance in Aedes aegypti. These findings demonstrate the diversity of detoxification mechanisms that can occur in Aedes, but since temefos is not pyrethroids, the results should not be treated as direct evidence of pyrethroid resistance mechanisms. Age differences and exposure patterns also need to be considered when interpreting susceptibility to deltamethrin (Al Nazawi & Weetman, 2023).

Thus, pyrethroid strategies combined with PBO cannot be assumed to be successful in all populations. More informative examinations combine mortality testing or bioassay, KDR markers, and metabolic mechanism information to ensure insecticide selection matches local resistance profiles.

Implications of KDR Mutation on Vector Control

An increase in the proportion of mosquitoes capable of surviving after pyrethroid exposure has the potential to reduce the benefits of chemical interventions and maintain the spread of resistant alleles in the population. However, "detected resistance" and "control failures in the field" are two different outcomes. Conclusions regarding program failures should consider the level of exposure, the application of the dosage according to the guidelines, the scope of spraying, environmental conditions, the size of the mosquito population, and the data on the outcome of the intervention. The synthesized study is more strongly supportive of the existence and mechanisms of resistance than providing quantitative measures of program failure in different countries.

To support the control of dengue and other arboviruses, insecticide selection should take into account the results of local susceptibility tests and resistance management, including rotation of insecticide classes when appropriate to technical policies and the availability of alternatives. Chemical interventions need to be combined with breeding site reduction, environmental management, larval eradication, and community involvement in vector monitoring. These strategies are in line with the integrated vector management approach discussed in the literature (Francis et al., 2021; Rodríguez et al., 2020).

Study Limitations

This synthesis was limited to 14 selected publications with non-uniform designs, regions, species, and resistance indicators. Information on the elimination of duplication, detailed reasons for exclusion, and risk assessment of bias for each publication was not available in the

summarized selection record. Therefore, this study did not claim to meet all components of the PRISMA systematic review, nor did it conduct a combined meta-analysis or quantitative estimate. Generalization of findings and claims of causal relationship with operational failure needs to be done carefully.

CONCLUSION

The synthesis of 14 publications published between 2018 and 2025 indicates that knockdown resistance (kdr) mutations in Aedes mosquitoes are geographically widespread and occur in both Aedes aegypti and Aedes albopictus, with F1534C, V1016G, V1016I, V410L, S989P, and I1532T representing the principal variants of concern in the reviewed literature. The evidence demonstrates that kdr mutations are unevenly distributed across geographic regions and mosquito species, with studies from Africa documenting V1016I and V410L variants, studies from Asia reporting associations between V1016G and F1534C and reduced pyrethroid susceptibility, and studies from the Americas identifying multiple coexisting resistance mechanisms. The literature further indicates that combinations of mutations at multiple loci, particularly F1534C occurring alongside V1016G, V410L, or S989P, may be associated with stronger resistance phenotypes than individual substitutions, although these findings cannot be generalized across mosquito populations without local validation. Importantly, the synthesis reveals that voltage-gated sodium channel (VGSC) target-site mutations frequently coexist with metabolic detoxification mechanisms and that synergism with piperonyl butoxide (PBO) does not consistently restore pyrethroid susceptibility. These findings underscore the importance of integrating molecular diagnostics with phenotypic bioassays to achieve a comprehensive characterization of insecticide resistance. However, the review also highlights a critical distinction between laboratory-detected insecticide resistance and operational failures in vector control programs. The synthesized evidence provides stronger support for the occurrence and underlying mechanisms of resistance than for quantitative assessments of vector control failures across countries. Furthermore, the limited number of included publications, heterogeneity in study designs, and insufficient documentation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedures limit the strength of causal inferences and preclude reliable meta-analytic estimates. Consequently, the findings should be interpreted cautiously, particularly when extrapolating laboratory-based resistance patterns to operational vector control outcomes.

Future research should prioritize the development and adoption of standardized protocols for kdr mutation surveillance that integrate allele frequency data with quantitative phenotypic resistance indicators, including median lethal concentration (LC_{50}) values, where appropriate, and mosquito mortality rates obtained through World Health Organization (WHO) tube tests and Centers for Disease Control and Prevention (CDC) bottle bioassays. Such standardization would facilitate cross-study comparisons and pooled analyses. Further investigations should examine the functional consequences of combinations of VGSC mutations through site-directed mutagenesis and electrophysiological characterization to

establish causal relationships between specific mutation combinations and altered pyrethroid sensitivity, rather than relying exclusively on correlations observed in field populations. Additionally, longitudinal surveillance studies are needed to monitor the emergence, geographic spread, and temporal dynamics of kdr variants in sentinel mosquito populations, particularly in areas characterized by substantial human mobility, such as ports and major urban transportation hubs. These investigations could support the development of early warning systems and adaptive insecticide resistance management strategies. Future studies should also systematically assess the operational implications of kdr mutations by integrating molecular and phenotypic resistance data with entomological outcomes from field-based vector control interventions. Relevant indicators include mosquito mortality following insecticide application, the residual efficacy of insecticide-treated surfaces, and associations between resistance patterns and arboviral disease incidence, while accounting for potential epidemiological and environmental confounders. Furthermore, the development and validation of rapid, field-deployable molecular diagnostic assays for kdr genotyping could improve the feasibility and accessibility of routine insecticide resistance surveillance in resource-limited endemic settings. Subsequent research should evaluate the diagnostic accuracy, cost-effectiveness, operational feasibility, and programmatic utility of these tools within integrated vector management frameworks to strengthen evidence-based insecticide resistance monitoring and inform sustainable vector control strategies.

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CONFLICT OF INTEREST

The author declares that there are no personal, commercial, or financial conflicts of interest that could influence the conduct or findings of this research.

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GENERATIVE ARTIFICIAL INTELLIGENCE USAGE STATEMENT

During the preparation of this article, the author used generative artificial intelligence (AI) as an assistive tool to improve language clarity, organize the manuscript structure, and refine grammar. The use of AI was limited and remained under the author's supervision. All data, analyses, interpretations, and scientific content presented in this article were carefully reviewed and verified by the author. The author assumes full responsibility for the accuracy, originality, and final content of the manuscript.

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