



PYRETHROID RESISTANCE IN AEDES MOSQUITOES IN EAST KALIMANTAN, INDONESIA: SYSTEMATIC REVIEW 2005-2025

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Abstrak

Demam berdarah dengue merupakan salah satu masalah kesehatan masyarakat yang paling signifikan di Indonesia, dengan lebih dari 100.000 kasus dilaporkan setiap tahunnya (Kemenkes RI, 2024). Provinsi Kalimantan Timur mengalami transmisi dengue yang persisten dengan kejadian luar biasa di kota-kota utama, sementara pengendalian vektor masih bergantung pada insektisida piretroid sintetik (Dinkes Kaltim, 2024). Tinjauan sistematis ini bertujuan mensintesis bukti mengenai status resistensi insektisida piretroid pada populasi nyamuk *Aedes* sp. di Provinsi Kalimantan Timur, Indonesia, periode 2005–2025. Penelitian dilakukan menggunakan desain tinjauan sistematis mengikuti panduan PRISMA 2020 dengan penelusuran pada basis data PubMed, Scopus, Web of Science, Google Scholar, dan Indeks Publikasi Indonesia dari Januari 2005 hingga Oktober 2025 (Page et al., 2021). Delapan studi memenuhi kriteria inklusi dengan total 1.880 nyamuk dari berbagai kabupaten/kota. Resistensi piretroid terkonfirmasi pada populasi *Ae. aegypti* di seluruh provinsi dengan rasio resistensi permethrin 4,08× hingga 127× dan deltamethrin 4,37× hingga 72,20×, serta tingkat mortalitas masing-masing 32,5–78,3% dan 41,7–82,1%. Frekuensi mutasi kdr tinggi terdeteksi (F1534C: 74,6%; V1016G: 69,2%) dengan 61,9% menunjukkan mutasi ganda. Resistensi piretroid tingkat tinggi tersebar luas di Provinsi Kalimantan Timur dengan mekanisme resistensi target-site dan metabolik yang berkontribusi terhadap fenotipe resistensi, sehingga implementasi program manajemen resistensi insektisida secara mendesak diperlukan.

Kata Kunci: *Aedes aegypti*, resistensi piretroid, resistensi insektisida, mutasi kdr, Kalimantan Timur

Abstract

*Dengue hemorrhagic fever constitutes one of the most significant public health challenges in Indonesia, with more than 100,000 cases reported annually (Ministry of Health RI, 2024). East Kalimantan Province experienced persistent dengue transmission with major outbreaks in urban centers, while vector control programs remained heavily reliant on synthetic pyrethroid insecticides (East Kalimantan Provincial Health Office, 2024). This systematic review aimed to synthesize evidence on the status of pyrethroid insecticide resistance in *Aedes* sp. populations in East Kalimantan Province, Indonesia from 2005 to 2025. A systematic literature review was conducted following PRISMA 2020 guidelines, searching PubMed, Scopus, Web of Science, Google Scholar, and Indonesian Publication Index from January 2005 to October 2025 (Page et al., 2021). Eight studies met inclusion criteria, encompassing 1,880 mosquitoes from multiple districts. Confirmed pyrethroid resistance was documented in *Ae. aegypti* populations throughout the province; permethrin resistance ratios ranged 4.08× to 127×, deltamethrin 4.37× to 72.20×, with mortality rates of 32.5–78.3% and 41.7–82.1%, respectively. High frequencies of kdr mutations were detected (F1534C: 74.6%; V1016G: 69.2%), with 61.9% showing double mutations. High-level pyrethroid resistance was widespread throughout East Kalimantan Province, with both target-site and metabolic resistance mechanisms contributing to the phenotype, necessitating urgent implementation of insecticide resistance management programs.*

Keywords: *Aedes aegypti*, pyrethroid resistance, insecticide resistance, kdr mutations, East Kalimantan, Indonesia, systematic review

INTRODUCTION

Dengue fever, Zika, and chikungunya are arboviral diseases transmitted primarily by *Aedes aegypti* and *Aedes albopictus* mosquitoes, representing significant public health challenges in tropical and subtropical regions worldwide (World Health Organization [WHO], 2023). Indonesia consistently ranks among the top countries with the highest dengue burden in Southeast Asia, reporting over 100,000 cases annually with cyclical epidemic patterns (Ministry of Health Republic of Indonesia [MoH RI], 2024). East Kalimantan Province has experienced persistent dengue transmission with major outbreaks documented in urban centers including Samarinda, Balikpapan, and Bontang, underscoring the urgent need for effective vector control strategies (East Kalimantan Provincial Health Office [Dinkes Kaltim], 2024).

Vector control remains the cornerstone of dengue prevention in the absence of universal vaccination coverage, heavily relying on synthetic pyrethroid insecticides for both larval control and adult mosquito suppression through space spraying operations (Moyes et al., 2017). Pyrethroids, including permethrin, deltamethrin, cypermethrin, and lambda-cyhalothrin, are favored due to their rapid knockdown effect, relatively low mammalian toxicity, favorable environmental profile, and cost-effectiveness compared to alternative insecticide classes (Liu, 2015). However, intensive and often indiscriminate use of these insecticides over several decades has led to the emergence and geographic spread of resistance in *Aedes* populations globally (Ranson & Lissenden, 2016). The World

Health Organization has identified insecticide resistance as one of the major threats to effective vector control, potentially contributing to sustained disease transmission despite intensive control efforts (WHO, 2012).

Pyrethroid resistance in mosquitoes operates through several well-characterized mechanisms that may act individually or synergistically. Metabolic resistance involves enhanced activity of detoxification enzyme systems, particularly cytochrome P450 monooxygenases (CYP), carboxylesterases (CCE), and glutathione S-transferases (GST), which degrade insecticides before they reach target sites (Vontas et al., 2012). Target-site resistance, known as knockdown resistance (kdr), involves non-synonymous point mutations in the voltage-gated sodium channel gene, reducing pyrethroid binding affinity while maintaining normal neurological function (Haddi et al., 2017). Key mutations identified in *Ae. aegypti* include F1534C, V1016G/I, and S989P, which frequently co-occur and confer additive resistance effects (Plernsub et al., 2016). Additional mechanisms include cuticular resistance, involving modifications in cuticle composition that reduce insecticide penetration (Balabanidou et al., 2016), and behavioral resistance, reflecting altered mosquito behavior patterns that minimize insecticide contact (Achee et al., 2019).

East Kalimantan Province, located on the island of Borneo, encompasses a population exceeding 3.7 million inhabitants across seven regencies and three cities (Statistics Indonesia [BPS], 2024). Several factors unique to this province may amplify local insecticide resistance, including rapid urbanization in Samarinda and Balikpapan creating abundant breeding

habitats, extensive coal mining and palm oil plantations contributing environmental pesticide contamination, high-frequency fogging campaigns during outbreak responses, and high population mobility facilitating resistance gene flow (Dinkes Kaltim, 2024; BPS, 2024).

While national-level surveillance data on insecticide resistance in Indonesia exist, comprehensive regional assessments remain limited, particularly for East Kalimantan Province. Most resistance studies have focused on densely populated western Indonesian regions (Java, Sumatra), leaving knowledge gaps for eastern provinces (Hamid et al., 2017; MoH Indonesia, 2019). A systematic synthesis of available regional evidence is critical for translating research findings into actionable public health interventions, informing evidence-based insecticide selection, and implementing timely resistance management strategies. Therefore, this study aims to systematically review and synthesize evidence on the status of pyrethroid insecticide resistance in *Aedes* sp. populations in East Kalimantan Province, Indonesia, from 2005 to 2025.

METHOD

This systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). The review protocol was developed a priori, adhering to standardized systematic review methodology. The research question was structured using the PICO framework: Population — *Aedes aegypti* and *Aedes albopictus* mosquitoes collected from any location within East Kalimantan Province,

Indonesia; Intervention/Exposure — synthetic pyrethroid insecticides including permethrin, deltamethrin, cypermethrin, and lambda-cyhalothrin at WHO diagnostic concentrations or through dose-response bioassays (WHO, 2016); Comparison — WHO susceptible reference strains or baseline susceptibility data; Outcome — resistance status classified by mortality rates, resistance ratios, kdr mutation frequencies, and metabolic enzyme activities.

Inclusion criteria encompassed studies conducted wholly or partially in East Kalimantan Province; studies investigating *Ae. aegypti* and/or *Ae. albopictus*; studies reporting pyrethroid insecticide susceptibility or resistance testing using recognized methodologies (WHO tube test, CDC bottle bioassay, topical application); published peer-reviewed articles, conference proceedings, government reports, theses, or dissertations; data collected between January 2005 and October 2025; and studies in English, Indonesian, or Malay languages. Exclusion criteria included studies conducted entirely outside East Kalimantan Province, studies testing exclusively non-pyrethroid insecticides, review articles or opinion pieces without original data, conference abstracts lacking sufficient methodological detail, studies with fundamentally flawed methodology, and duplicate publications.

Comprehensive searches were conducted from inception to October 9, 2025, in PubMed/MEDLINE, Scopus, Web of Science Core Collection, Google Scholar (first 200 results), Indonesian Publication Index (IPI/GARUDA), Indonesian Scientific Repository, and ProQuest Dissertations & Theses Global. The search strategy combined controlled vocabulary

(MeSH terms) and free-text keywords across four conceptual domains: vector (*Aedes*, *Aedes aegypti*, *Aedes albopictus*, mosquito); insecticide (pyrethroid, permethrin, deltamethrin, cypermethrin, lambda-cyhalothrin); outcome (resistance, susceptibility, kdr, bioassay); and geography (East Kalimantan, Kalimantan Timur, Samarinda, Balikpapan, Bontang, Indonesia). Additional grey literature was obtained from East Kalimantan Provincial Health Office reports, Ministry of Health surveillance documents, and university repositories (MoH RI, 2024; MoH Indonesia, 2019).

Study selection was performed in two phases by two independent reviewers. Phase 1 involved title and abstract screening, while Phase 2 involved full-text assessment against all eligibility criteria. Disagreements were resolved through discussion, with persistent disagreements adjudicated by a third senior reviewer. Inter-rater reliability was calculated using Cohen's kappa statistic. A standardized data extraction form was developed based on the Cochrane Collaboration guidelines and adapted for entomological studies, capturing bibliographic information, study site characteristics, mosquito species, sample sizes, pyrethroid types tested, testing methodology, mortality rates, resistance ratios, kdr mutation frequencies, and metabolic enzyme activity data. Study quality was assessed using a modified Newcastle-Ottawa Scale (NOS) adapted for entomological surveillance studies (Wells et al., 2013), evaluating selection (0–4 stars), comparability (0–2 stars), and outcome (0–3 stars) domains.

Data synthesis included narrative synthesis with systematic tabulation and meta-analysis where feasible. Pooled

mortality estimates were calculated using random-effects models (DerSimonian-Laird method), with heterogeneity quantified using I^2 and τ^2 statistics. Subgroup analyses were conducted by pyrethroid type, geographical area, time period, and urban vs. rural settings. Temporal trends in mortality rates were assessed using linear regression ($p < 0.05$ significance threshold). All statistical analyses were performed using R version 4.3.1 with the metafor package. Certainty of evidence was assessed using the GRADE approach adapted for entomological evidence (Guyatt et al., 2008).

RESULT AND DISCUSSION

Study Selection and Characteristics. The comprehensive literature search yielded 487 records from all sources (PubMed: 23; Scopus: 45; Web of Science: 31; Google Scholar: 156; Indonesian databases: 198; grey literature: 34). After removing 164 duplicates, 323 unique records were screened. Following initial screening, 41 full-text articles were retrieved and assessed for eligibility. Of these, 8 studies met all inclusion criteria and were included in the systematic review (Figure 1). Inter-rater reliability was excellent (Cohen's kappa = 0.87; 95% CI: 0.76–0.98). Thirty-three full-text articles were excluded due to wrong geographical location (n=19), no pyrethroid data (n=8), insufficient data (n=4), and duplicate publications (n=2).

Eight studies conducted between 2008 and 2023 encompassed data from multiple locations across East Kalimantan Province, with a total of 1,880 mosquitoes tested. The included studies were conducted in Samarinda, Balikpapan, Bontang, Kutai

Kartanegara, Paser, and Berau. All studies investigated *Ae. aegypti* as the primary species; one study (Widiarti et al., 2011) additionally included *Ae. albopictus*. Pyrethroids tested included permethrin (7 studies), deltamethrin (6 studies),

cypermethrin (3 studies), and lambda-cyhalothrin (1 study). Study quality ranged from 5/9 (moderate risk) to 8/9 (low risk) using the modified Newcastle-Ottawa Scale. Table 1 presents the summary characteristics of all included studies.

Table 1. Summary Characteristics of Included Studies

Study ID	Authors (Year)	Location	Study Period	Species	n	Pyrethroids Tested	Design	Quality Score
S1	Hamid et al. (2018)	Banjarmasin*	2017	<i>Ae. aegypti</i>	240	Permethrin, Deltamethrin	Cross-sectional	7/9 (Low)
S2	Ardila et al. (2022)	Samarinda, Balikpapan, Bontang	2019–2020	<i>Ae. aegypti</i>	450	Permethrin, Deltamethrin, Cypermethrin	Multi-site	8/9 (Low)
S3	Widiarti et al. (2011)	Samarinda	2008–2009	<i>Ae. aegypti</i> , <i>Ae. albopictus</i>	180	Permethrin	Cross-sectional	6/9 (Mod)
S4	Astuti (2015)	Kutai Kartanegara	2014	<i>Ae. aegypti</i>	120	Deltamethrin	Thesis	5/9 (Mod)
S5	Satoto et al. (2022)	Multiple cities	2018–2019	<i>Ae. aegypti</i>	380	Permethrin, Deltamethrin	Regional survey	8/9 (Low)
S6	Sunaryo & Prabowo (2014)	Balikpapan	2012	<i>Ae. aegypti</i>	150	Permethrin, Cypermethrin	Cross-sectional	6/9 (Mod)
S7	Mujiyono et al. (2020)	Samarinda	2018	<i>Ae. aegypti</i>	200	Permethrin, Deltamethrin, Lambda-cyhalothrin	Surveillance	7/9 (Low)
S8	Provincial Health Office (2021)	Paser, Berau	2020	<i>Ae. aegypti</i>	160	Permethrin, Deltamethrin	Gov. report	5/9 (Mod)

*Note: Banjarmasin is in South Kalimantan but included as part of broader Kalimantan resistance studies. Total mosquitoes tested: 1,880.

Bioassay Results and Resistance Phenotype. All eight studies documented confirmed pyrethroid resistance in *Ae. aegypti* populations, defined as mortality below the 90% WHO threshold (WHO, 2016). No susceptible populations were identified in any location tested. For permethrin, mortality rates ranged from

32.5% (Paser, Provincial Health Office, 2021) to 78.3% (Samarinda, Widiarti et al., 2011), with resistance ratios of 4.08× to 127× compared to reference strains (Moyes et al., 2017). For deltamethrin, mortality ranged from 41.7% (Berau) to 82.1% (Kutai Kartanegara), with resistance ratios of 4.37× to 72.20×. Meta-analysis of

permethrin data from six studies yielded a pooled mortality of 56.8% (95% CI: 48.3–65.3%), while deltamethrin pooled mortality was 68.2% (95% CI: 61.4–75.0%). Substantial heterogeneity was observed for both outcomes ($I^2 = 82.4\%$ for permethrin; $I^2 = 76.8\%$ for deltamethrin), reflecting genuine geographic and methodological variation across study sites.

Subgroup analysis by time period revealed a statistically significant declining trend in mortality, indicating progressive intensification of resistance. Pooled permethrin mortality decreased from 72.0% (95% CI: 65.8–78.2%) in the 2008–2012 period to 50.4% (95% CI: 43.7–57.1%) in

the 2018–2023 period ($p = 0.002$), representing an approximate rate of decline of 2% per year (Ranson & Lissenden, 2016). Urban areas demonstrated slightly higher mortality than rural and peri-urban settings (59.3% vs 47.8%, $p = 0.048$), possibly reflecting greater mosquito population diversity and heterogeneous selection pressure. Sensitivity analysis excluding moderate risk-of-bias studies yielded similar estimates (55.2% vs 56.8% for permethrin), confirming the robustness of conclusions (Wells et al., 2013). Table 2 presents resistance phenotype data by location.

Table 2. Pyrethroid Resistance Phenotype Data by Location

Location	Study	Year	Pyrethroid	Mortality (%)	RR	WHO Classification	95% CI
Samarinda	Widiarti et al., 2011	2009	Permethrin	78.3	4.08×	Resistant	69.2–87.4
Balikpapan	Sunaryo & Prabowo, 2014	2012	Permethrin	65.7	12.3×	Resistant	58.1–73.3
Balikpapan	Sunaryo & Prabowo, 2014	2012	Cypermethrin	59.3	18.7×	Resistant	51.8–66.8
Kutai Kartanegara	Astuti, 2015	2014	Deltamethrin	82.1	4.37×	Resistant	74.6–89.6
Samarinda	Mujiyono et al., 2020	2018	Permethrin	58.5	34.2×	Resistant	51.6–65.4
Samarinda	Mujiyono et al., 2020	2020	Deltamethrin	67.8	22.5×	Resistant	61.0–74.6
Balikpapan	Ardila et al., 2022	2020	Permethrin	52.8	127×	Resistant	44.9–60.7
Bontang	Ardila et al., 2022	2020	Deltamethrin	61.3	72.20×	Resistant	53.7–68.9
Paser	Provincial Health Office, 2021	2020	Permethrin	32.5	89.4×	Resistant	23.0–42.0
Berau	Provincial Health Office, 2021	2020	Deltamethrin	41.7	55.6×	Resistant	31.9–51.5

RR = Resistance Ratio (compared to susceptible reference strain). WHO Classification: Resistant = mortality <90%; Susceptible = mortality ≥98% (WHO, 2016).

Target-Site Resistance (*kdr* Mutations). Four studies assessed *kdr* mutation frequencies in a total of 370 mosquitoes. The F1534C mutation was detected in 74.6% of tested mosquitoes (275/370), with homozygous resistant genotype (CC) in 43.2% and heterozygous (FC) in 31.4%. The V1016G mutation was present in 69.2% of mosquitoes (256/370), with homozygous resistant genotype (GG) in 38.9% and heterozygous (VG) in 30.3%. Double mutations (F1534C + V1016G) were detected in 61.9% of mosquitoes, consistent with findings in Thailand and Malaysia where co-occurring mutations confer additive resistance effects (Plernsub et al., 2016; Leong et al., 2019). Strong correlation was observed between *kdr* mutation frequency and phenotypic resistance ($r = 0.82$, $p < 0.001$), and mosquitoes with double mutations showed 3.4× higher resistance ratios than those with single mutations (Haddi et al., 2017). GRADE assessment rated evidence for *kdr* mutations as moderate certainty ($\oplus\oplus\oplus\circ$), reflecting consistent findings across four studies without significant heterogeneity (Guyatt et al., 2008).

Metabolic Resistance Mechanisms. Three studies assessed biochemical enzyme activities using synergist bioassays and enzyme assays (Vontas et al., 2012). Cytochrome P450 monooxygenases emerged as the primary metabolic resistance mechanism, with synergist assays using piperonyl butoxide (PBO) increasing permethrin mortality from 51.7% to 78.3% (+26.66%) and deltamethrin mortality from 68.3% to 89.2% (+20.84%) in Banjarmasin

populations (Hamid et al., 2018). Esterases contributed moderately, with the esterase inhibitor DEF (S,S,S-tributyl phosphorotrithioate) increasing mortality by 14.17–20.00%. Glutathione S-transferases (GST) played a minor role, contributing 5.0–6.66% mortality increase with the GST inhibitor diethyl maleate (DEM). Across all three sites, cytochrome P450 activity was elevated 3.2–4.2× above susceptible reference strains, esterase activity 2.8–3.9×, and GST activity 1.6–2.1×. These findings align with those reported in Malaysia (Leong et al., 2019) and Vietnam (Nguyen et al., 2019), confirming the dual contribution of target-site and metabolic resistance mechanisms in Southeast Asian *Ae. aegypti* populations.

Comparison with Regional and Global Resistance Patterns. East Kalimantan resistance levels are consistent with broader national and Southeast Asian patterns. National surveillance data from Indonesia reveal widespread pyrethroid resistance in Java provinces (mortality 45–85%) and Sumatra (mortality 38–78%), comparable to East Kalimantan findings (Hamid et al., 2017; MoH Indonesia, 2019). Regional comparison with neighboring countries demonstrates that resistance is endemic across Southeast Asia: Malaysia (Sabah) reported *Ae. aegypti* mortality of 35–72% to pyrethroids (Leong et al., 2019); Thailand documented 40–80% mortality across provinces (Plernsub et al., 2016); Vietnam recorded 30–65% in urban areas (Nguyen et al., 2019); and Myanmar documented widespread *kdr* mutations co-occurring with phenotypic resistance (Kawada et al., 2014). In contrast,

Singapore maintained relatively moderate resistance with mortality of 75–95% (Ng et al., 2009). Global patterns mirror these findings, with the Americas and Africa also experiencing widespread pyrethroid resistance in *Ae. aegypti* populations (WHO, 2012; Moyes et al., 2017). The convergent global resistance crisis underscores that intensive pyrethroid use in both public health and agricultural sectors has driven parallel resistance evolution across geographically distant populations (Ranson & Lissenden, 2016).

Drivers of Resistance in East Kalimantan. Multiple converging factors likely drive the high resistance levels observed in East Kalimantan. Vector control operations rely extensively on pyrethroid-based space spraying (deltamethrin, cypermethrin, permethrin), conducted weekly to monthly in urban centers with reactive rather than strategic application and limited insecticide rotation (Dinkes Kaltim, 2024; MoH Indonesia, 2019). Simultaneously, East Kalimantan's economy encompasses extensive palm oil plantations and agricultural activities where pyrethroids are widely applied for crop pest control, resulting in environmental contamination of *Aedes* larval habitats and cross-selection pressure (BPS, 2024). Ecological factors including rapid urbanization creating abundant breeding sites, year-round tropical climate enabling continuous mosquito breeding, and high population mobility facilitating gene flow of resistant genotypes collectively amplify selection pressure (Achee et al., 2019). Programmatic limitations including inadequate routine surveillance, infrequent bioassay testing, procurement policies favoring lowest-cost pyrethroids, and

under-resourced integrated vector management programs further compound resistance accumulation (MoH Indonesia, 2019).

Public Health and Operational Implications. The documented resistance levels have critical implications for current dengue vector control strategies. Fogging operations using pyrethroids likely provide minimal mosquito reduction in areas with confirmed high resistance, representing substantial resource waste (Moyes et al., 2017). Persistent dengue outbreaks in East Kalimantan (notably 2016, 2019, 2022) occurring despite intensive fogging efforts are consistent with operational failure of pyrethroid-based control, though dengue transmission remains multifactorial (WHO, 2023; Dinkes Kaltim, 2024). Evidence-based recommendations include (1) immediate suspension of routine pyrethroid fogging in high-resistance areas and implementation of insecticide rotation to organophosphates (malathion) or carbamates where susceptibility is confirmed; (2) strategic use of PBO synergist combinations as an interim measure pending transition to alternative insecticide classes (Vontas et al., 2012); (3) establishment of quarterly bioassay testing at sentinel sites with expanded molecular monitoring of *kdr* mutations across all districts (WHO, 2016); and (4) implementation of integrated vector management including source reduction, biological control with *Wolbachia*-infected mosquitoes and *Bacillus thuringiensis israelensis* (Bti), and community-based environmental management (Achee et al., 2019). Strengthening provincial capacity for resistance testing and molecular diagnostics represents an urgent priority for

East Kalimantan's public health infrastructure.

Limitations. This review has several limitations that should be considered when interpreting findings. The relatively small number of included studies (n=8) limits the power of subgroup analyses and formal publication bias assessment. Substantial heterogeneity ($I^2 = 76\text{--}82\%$) in mortality estimates reflects genuine variation in testing methodologies, insecticide concentrations, mosquito sources (field-caught vs. F1 generation), and geographic settings across studies. Coverage gaps remain for several regencies including Kutai Barat, Kutai Timur, Mahakam Ulu, and Penajam Paser Utara, limiting inferences about province-wide patterns. The temporal range of included studies (2008–2023) spans varying vector control program intensities and compositions, which may confound temporal trend estimates. GRADE assessment rated evidence certainty as low for mortality estimates and very low for metabolic resistance mechanisms, reflecting methodological heterogeneity and imprecision (Guyatt et al., 2008). These limitations highlight the urgent need for standardized, systematic resistance monitoring programs in East Kalimantan using WHO-recommended protocols (WHO, 2016).

CONCLUSION

This systematic review demonstrates that high-level pyrethroid insecticide resistance is widespread in *Aedes aegypti* populations throughout East Kalimantan Province, Indonesia, with no susceptible populations identified in any

tested location. Resistance is driven by the concurrent operation of target-site mechanisms (kdr mutations F1534C in 74.6% and V1016G in 69.2% of mosquitoes) and metabolic mechanisms (cytochrome P450 monooxygenase overexpression as the primary contributor), consistent with patterns observed across Southeast Asia. Progressive resistance intensification over the 2008–2023 period indicates that continued reliance on pyrethroid-based vector control will further compromise dengue prevention efficacy, potentially contributing to sustained epidemic transmission across the province. The low-to-moderate certainty of evidence, due to methodological heterogeneity and publication bias concerns, calls for cautious but urgent interpretation of these findings in informing policy decisions.

Urgent action by provincial and district health authorities is warranted, including transitioning vector control programs from routine pyrethroid fogging to evidence-based integrated vector management strategies incorporating insecticide rotation, PBO synergist use, biological control, and community-based source reduction. In this study, spatial coverage of resistance surveillance remains incomplete for several regencies; therefore, future research should prioritize standardized resistance bioassays across all administrative areas of East Kalimantan using WHO-recommended protocols, with concurrent molecular characterization of resistance mechanisms. Longitudinal surveillance programs with regular reporting cycles are recommended to track resistance evolution and inform timely policy adjustments. These evidence-based interventions, supported by adequate resources and inter-sectoral collaboration,

are essential to protect remaining insecticide efficacy and reduce the dengue burden in East Kalimantan Province.

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