Journal of Chemical Health Risks

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JCHR (2024) 14(1), 430-443 | ISSN:2251-6727

Trends and Research Hotspots of Knockdown Resistance in the Aedes Genus in Indonesia: A Bibliometric Surveillance from the Scopus Database

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(Received: 27 October 2023 Revised: 22 November Accepted: 26 December)

KEYWORDS
Knockdown resistance;
Aedes Genus;
Indonesia;
One Health;
Disease Burden.

ABSTRACT:

Introduction: Knockdown resistance in the Aedes genus in Indonesia is increasing; however, a comprehensive analysis of trends and research hotspots has not been reported.

Objectives: This study aimed to analyze the trends and research hotspots of knockdown resistance in the Aedes genus in Indonesia using bibliometric surveillance, focusing on information from the Scopus database.

Methods: Various keywords and databases were used to screen the articles, and all the articles obtained were analyzed using network, overlay, and density visualization using VOSviewer software version 1.6.20.

Results: The findings showed that 14 articles were identified, resulting in 86 terms corresponding to the topic of this study, forming six main clusters of 1,496 links with 7,188 links. *Aedes albopictus* and *Aedes aegypti* have been reported to be resistant to the Aedes genus. The types of insecticides reported and suspected to cause kdr are pirimiphos methyl, cyfluthrin, piperonyl butoxide, cyhalothrin, cypermermethrin, transflutrin, temephos, malathion, organophosphates and fenitrothion. For the intended kdr target, alleles affected by these conditions occurred in f1534c, l982w, s989p, v1023g, s996p, and others. The region with the highest reported kdr in the genus Aedes was Yogyakarta (central Java), followed by Bali (Denpasar) and Jakarta. The identification of kdr in the Aedes genus in Indonesia has focused on 'voltage-gated sodium channel' OR 'vgsc,' 'larvae,' and 'temephos,' which are research hotspots that have a high linkage of terms with other terms, while the phrases 'voltage sensitive sodium channel' OR 'vssc,' 'primary vector' and 'genotyping' are research coldspots characterized by links dominated by recent research.

Conclusions: There has been a significant increase in the incidence of kdr in the genus Aedes in Indonesia. This highlights the importance of focusing on understanding resistance mechanisms, exploring new control strategies, addressing geographic variation, and encouraging collaborative efforts to underscore the importance of a comprehensive approach to combating mosquito-borne diseases. This surveillance provides valuable insights for policymakers, researchers, and public health practitioners for formulating targeted interventions to mitigate the future impact of Aedes mosquito-borne diseases in Indonesia.

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JCHR (2024) 14(1), 430-443 | ISSN:2251-6727

1. Introduction

Indonesia is a tropical country with a high prevalence of mosquito-borne diseases. Every year, Indonesia experiences an increase in the number of cases of diseases transmitted by Aedes mosquitoes, such as dengue fever, chikungunya, and Zika [1–3]. This raises awareness and concerns about public health. Several efforts have been made to control this disease-carrying vector, such as implementing focused fooging, carrying out mosquito nest eradication *(PSN)* and 4 M plus (draining, covering, burying, monitoring, planting anti-mosquito plants, sowing larvicides, etc.) [4–6], and running the one-house, one larva monitor *(JUMANTIK)* program *(1R1J)* [7]. However, these efforts have not been able to run optimally, and mosquito populations are increasing[8]. In addition, insecticides have been used to eradicate vectors, especially mosquitoes; however, resistance issues have increased in some parts of Indonesia [9–11].

The overuse of insecticides in Indonesia has caused dengue mosquitoes to experience disease knockdown (kdr), making it difficult to control their populations and resulting in a greater risk of transmission and mortality [12,13]. Previous studies have investigated the prevalence and distribution of knockdown resistance in Aedes mosquitoes in Indonesia [10,14–16]. However, the information obtained tends to be diverse and limited. To date, there has been no comprehensive analysis of the trends and hotspots in this area. Therefore, to address this gap and fill the topic void related to current research trends and hotspots, we conducted a bibliometric survey focusing on information reported in the Scopus database for further analysis.

2. Objectives

The question proposed in this study is, what is the trend of knockdown resistance reports in the Aedes genus in Indonesia?.This study aimed to provide a comprehensive overview of the trends and research hotspots in the field of knockdown resistance in Aedes mosquitoes in Indonesia, which can serve as a basis for future public health research and interventions. Understanding trends, hotspots, coldspots, and highlighted terms can provide policymakers with information that can inform future public health research and interventions.

3. Methods

3.1 Study registration

This study was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA) guidelines [17,18], and the study protocol was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database with registration number CRD42023465281.

3.2 Study design

This study utilized a bibliometric method to investigate trends, identify research hotspots, and analyze the implications, policy directions, and future research related to knockdown resistance (kdr) in the Aedes genus in Indonesia. This approach was selected because it offers a comprehensive and quantifiable means of providing information on strategies and policies that can be implemented; mapping the evolution of research topics; and determining the direction of scientifically relevant concepts, networks, and strategies aimed at reducing the incidence of kdr in different regions of Indonesia [3].

3.3 Literature search strategy and study selection

A comprehensive literature search was independently conducted by two authors between July and September 2023. The search process utilized Publish or Perish (PoP) software to obtain articles from highly reputable journals published in the Scopus, PubMed, and Web of Science (WOS) databases. A set of keywords was employed using the Boolean operator guidelines for AND and OR. The keywords used in this study included ((["knockdown resistance" OR 'kdr", "Aedes", "Indonesia", "*Aedes aegypti*" OR "*A. aegypty*", "*Aedes albopictus*" OR "*A. albopictus*"]), (([["kdr", AND "Aedes", "resistance" AND "insecticide" AND "Deltamethrin" AND "Permethrin" AND "malathion" AND "sihalotrin" AND "bediocarb" AND "cyfluthrin" AND "siflotrin" AND "λ-cyhalothrin" AND "α-sipermethrin" AND "Temefos" AND "Alphacypermethrin"]])), ((([["kdr" AND "mutation" AND "allele" AND "VGSC" OR "voltage-gated sodium channel" AND "SS/VV/FF" OR "Wildtype" AND "PP/GG/CC" OR "Homozygot" AND "SP/VG/FC" OR "Heterozygot", "knockdown resistance" AND "Sumatra" OR "West Sumatra" OR "North Sumatra" OR "South Sumatra" OR "Riau" OR

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"Jambi" OR "Bengkulu" OR "Lampung" OR "Java" OR "West Java" OR "East Java" OR "Central Java" OR "Jakarta" OR "Surabaya" OR "Bandung" OR "Yogyakarta" OR "Java Islands" OR "Bali" OR "Denpasar" OR "Badung" OR "Gianyar" OR "Jembrana" OR "Singaraja OR "buleleng" OR "Karangasem" OR "Klungkung" OR "Tabanan" OR "Borneo" OR "East Kalimantan" OR "West Kalimantan" OR "South Kalimantan" OR "North Kalimantan" OR "Central Kalimantan" OR "Lombok" OR "West Nusa Tenggara" OR "Nusa Tenggara" OR "East Nusa Tenggara" OR "Sulawesi" OR "Central Sulawesi" OR "Southeast Sulawesi" OR "West Sulawesi" OR "South Sulawesi" OR "Gorontalo" OR "Makassar" OR "Kendari". All the articles obtained were then selected and analyzed based on their relevance, year of publication, topic studied, relevance to the research objectives, and comprehensive analysis of the article information.

3.4 Inclusion and exclusion criteria

Before beginning their research, the authors established inclusion and exclusion criteria to streamline the process and facilitate the literature search. In this particular investigation, the criteria for selecting articles deemed suitable for further analysis were as follows: articles published in Scopus (Quartiles 1–4), reputable indexed journals and/or indexed by the Web of Science with a core collection, written in English, and published within the last 10 years (2004–2023). Additionally, articles needed to focus on topics related to KDR in Indonesia and were derived from original articles, original research, and short communication and/or short reports. Articles that failed to meet these criteria, including those published in journals that were withdrawn from circulation, were excluded to maintain review integrity.

3.5 Data analysis and visualization

Mapping for this study was conducted by one author, while the results were interpreted by another author. The data were processed using VOSviewer software version 1.6.20, which allowed for the creation of datasets in research information systems (*RIS) format and CSV (.csv) files. At present, the visualization process involves the analysis of keyword co-occurrence networks, the tracking and mapping of keyword development over time via overlay visualization, and the assessment of keyword depth through density visualization. In our study, we examined the number of annual publications compared to the number of annual citations. Furthermore, we scrutinized the current and emerging areas of research to offer a comprehensive perspective on advanced research prospects. The data on keyword occurrence, number of cooccurrences along with the corresponding number of links, and total link strength are then analyzed based on the clustering of cooccurrences. The data were descriptively analyzed and presented in the form of narratives, tables, and figures.

4. Results

4.1 Search results and publication metrics

In this investigation, 37 articles were screened using predetermined keywords, but only 14 articles were selected for additional analysis owing to factors such as relevance, article type falling outside the specified range, language not being English, and other relevant considerations. All the articles obtained were published between 2004 and 2023, with 27.14 citations per year (acc1=5, acc2=5, acc5=5, acc10=2, acc20=0); 63.33, 570, 9.00, 1.00/1.0/1 (mean/median/mode); 52.34 (sqrt=7.23), 52.34/author and Hirsch h-indexes of 5 (a= 22.80, m= 0.24, 562 cites= 98.6% coverage); and an Egghe g-index of 9 (g/h= 1.80, 570 cites =100.0% coverage) with a PoP hI norm: 5 and a PoP hI annual: 0.24; and a Fassin hA index: 5. The results show that the impact of published papers has been quite high over the last 10 years.

4.2 Reputation of publication article

Based on the results of the analysis of 14 articles related to the Aedes genus in Indonesia, all of them were ranked as highly reputable journals indexed by Scopus and/or the Web of Science. The findings showed the distribution of articles indexed by Scopus quartile 1 (n = 8; 57.14%), quartile 2 (n = 1; 7.14%), quartile 3 (n = 4; 28.57%), and quartile 4 (n = 1; 7.14%). Furthermore, the types of publications were dominated by research articles (n = 10; 71.43%), original articles (n = 3; 21.43%), and short communications (n = 1; 7.14%). In terms of the distribution of journals that published articles related to kdr in the Aedes genus in Indonesia, most were from outside Indonesia (n = 8; 57.14%), and the rest were from Indonesia (n = 6; 42.85%). The Biodiversity and PloS journals are the authors' destinations for publishing their research results (n = 3; 21.43%), followed by the Parasites and Vectors journal (n = 2; 14.29) and the

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BioMed Research International Journal, Indonesian Biomedical Journal, Insects, Journal of Medical Entomology, and Journal of Tropical Biodiversity and Biotechnology (n = 1; 7.14).

The size of a highly reputable journal depends on the publishers that are not categorized as predatory publishers. This finding showed that nine (64.28%) publishers came from foreign publishers, whereas five (35.71%) came from Indonesia. This finding showed that four publishers (28.57%) were managed by universities, whereas 10 (71.42%) were managed by private institutions. The dominant publishers were the Public Library of Science, Springer Nature, and Sebelas Maret University Surakarta (n=3; 21.43%), Hindawi Publishing Corporation, Prodia Education and Research Institute, Multidisciplinary Digital Publishing Institute (MDPI), Oxford University Press, and Gadjah Mada University (n=1; 7.14). Finally, the reputation of articles depends on the number of publications produced each year and the number of citations obtained each year (Figure 1). The results showed that most documents related to the topic of kdr in the genus Aedes in Indonesia were published in 2018 (n = 3; 21.42%), and the highest number of citations was published in 2020 (n = 120), with an average number of citations per year (n = 38.22) from 2015 to 2023.

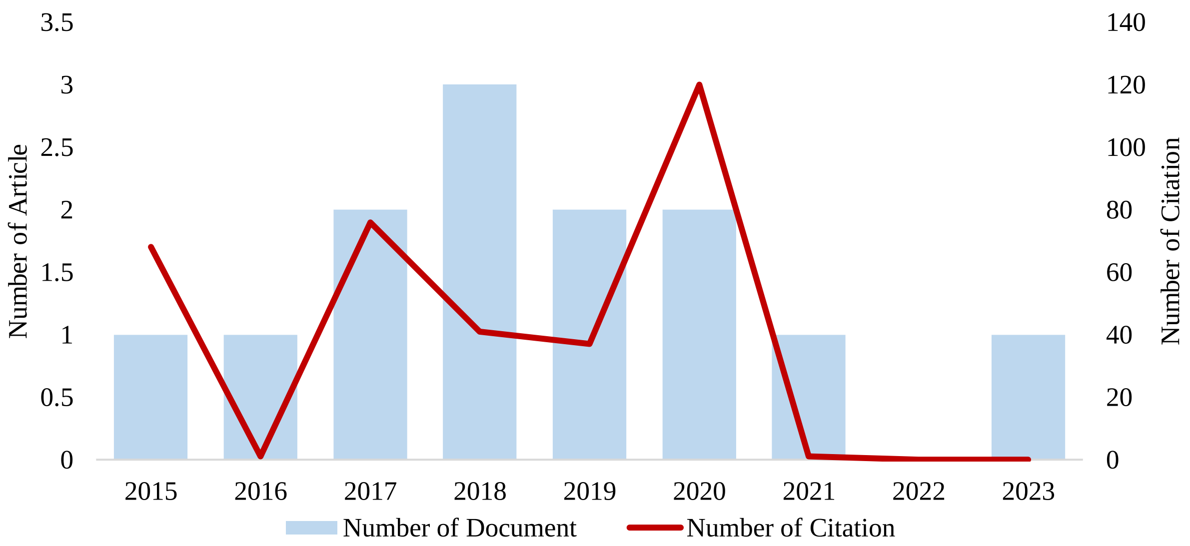

Figure 1. Comparison of the number of documents and citations of annual publications on knockdown resistance (kdr) reports in Indonesia

4.3 Network Visualization

Based on the analysis of network visualization using VOSviewer software and a minimum term selection of 10 studies, 8,584 terms related to kdr in the genus Aedes in Indonesia were obtained. Subsequently, the results were narrowed down based on relevance and met the threshold to produce 314 appropriate terms. Of these, 60% were deemed suitable for this study, leaving 86 terms for further examination. The study identified six clusters from 86 items, generating 1,496 networks with a total link strength of 7,188. Term clustering was performed by matching the topic of the discussion with the corresponding term in a published article. The terms that cooccurred are shown in Figure 2. The network visualization results showed that the term "Indonesia" generated the most nodes and occurrences, representing the region studied in this research (n = 307; link = 70; total link strength = 739). However, this term is located in cluster 3, which is relatively far from the main cluster. Furthermore, the terms "knockdown" (n = 123; link = 51; and total link strength = 217), "diptera" (n = 115; link = 73; and total link strength = 499), "culicidae" (n = 105; link = 68; and total link strength = 474), "repellent" (n = 49; link = 27; and total link strength = 148) and "repellency" (n = 30; link = 22; and total link strength = 130) were the most frequently occurring key terms or terms that were entered into Cluster 1.

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As evidenced by the literature, *Aedes albopictus* (n = 93; link = 56; total link strength = 320) and *Aedes aegypti* (n = 10; link = 19; total link strength = 34) are the most frequently studied species within the Aedes genus in relation to kdr. This is because these mosquito species are endemic to various regions across Indonesia, spanning from Sabang to Merauke. Moreover, we chose to focus on the types of insecticides that are commonly reported and suspected to lead to resistance (kdr) within the Aedes genus in Indonesia, namely, "pirimiphos methyl" (n = 10; link = 22; and total link strength = 61), "cyfluthrin" (n = 10; link = 33; and total link strength = 78), "piperonyl butoxide" (n = 16; link = 46; and total link strength = 159), "cyhalothrin" (n = 29; link = 41; and total link strength = 122), "cypermermethrin" (n = 14; link = 28; and total link strength = 83), "transflutrin" (n = 24; link = 28; and total link strength = 118), "temephos" (n = 38; link = 40; and total link strength = 287), "malathion" (n = 59; link = 60; and total link strength = 410), "organophosphate" (n = 31; link = 53; and total link strength = 230) and "fenitrothion" (n = 10; link = 30; and total link strength = 86).

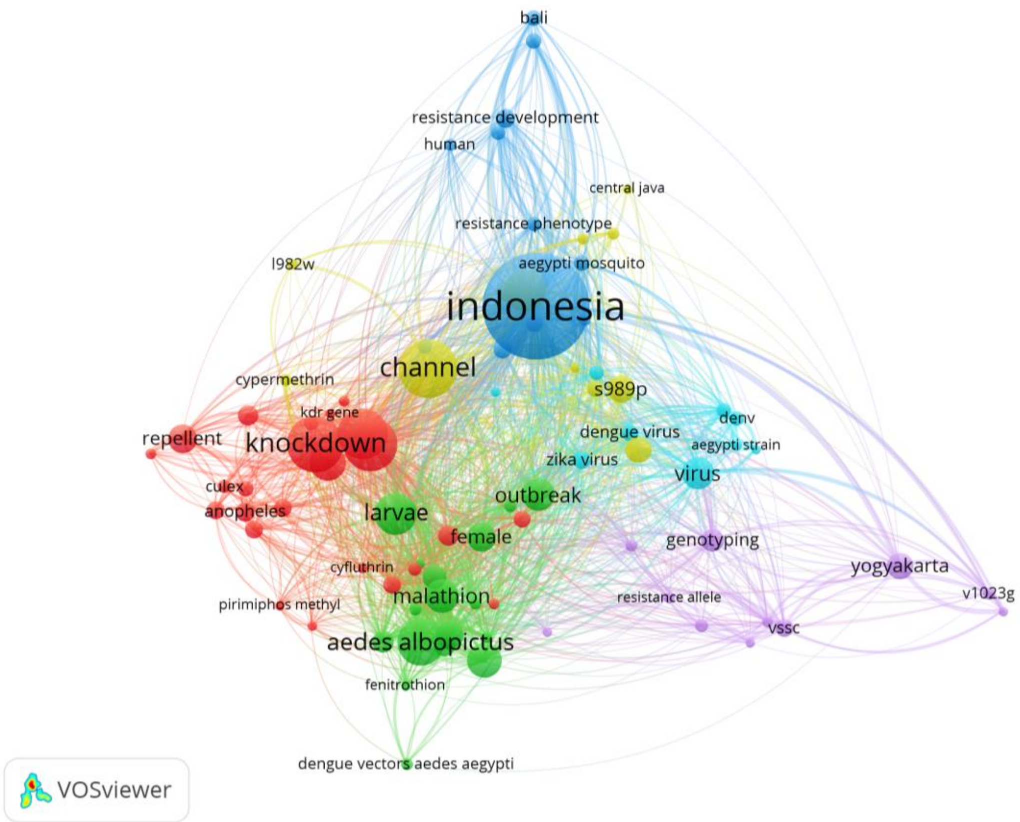

Figure 2. Co-occurring terms in articles published between 2004 and 2023 (n=6). The same color indicates the same cluster, whereas different colors indicate different clusters. The closer the nodes are to each other, the greater the co-occurrence (frequency) of keywords. The thickness of the line toward the node indicates that the recurrence and linkage of the topic have become stronger. Distances and nodes that are further away indicate that the relationships between the terms decrease and tend to be weak.

For the intended kdr target, alleles affected by kdr conditions were reported in 14 previous studies characterized by the phrases "f1534c kdr mutation" (n = 14; link = 36; and total link strength = 140), "l982w" (n = 13; link = 7; and total link strength = 43), "s989p" (n = 46; link = 57; and total link strength = 313), "v1023g" (n = 15; link = 14; and total link strength = 119), and "s996p" (n = 10; link = 10; total link strength = 104). The regions or provinces and/or districts in Indonesia with the most kdr reports in the Aedes genus were reported in the

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"Yogyakarta" region (n = 42; link = 31; and total link strength = 234), followed by "central java" (n = 10; link = 8; and total link strength = 22), "Bali" (n = 21; link = 17; and total link strength = 129), "Denpasar" (n = 21; link = 17; and total link strength = 186), and "Jakarta" (n = 18; link = 22; and total link strength = 137). Based on these findings, we highlight that only provinces classified as large cities (frequently visited areas) reported an incidence of kdr at the international level. Other areas may be reported but only on a national scale. A summary of the terms in each cluster, ordered from high to low, is presented in Table 1.

Table 1. Terms based on research clusters

Cluster (Items) - Color	Terms [Occurance]	Focus of research
Cluster 1 (24 items) - Red	Anopheles [27], c1534 [13], chemical [13], culex [17], culex quimquefasciatus [24], culicidae [105], cyfluthrin [10], cyhalothrin [29], deet [12], diptera [115], insecticide susceptibility status [11], kdr gene [11], knock [64], knockdown [123], malaria [25], malaria vector [20], mosquito coil [19], mosquito species [23], piperonyl butoxide [16], pirimiphos methyl [10], repellency [30], repellent [49], resistance ratio [24], transfluthrin [24].	Identification of knockdown resistance (kdr) to chemical insecticides in malaria-causing mosquito species
Cluster 2 (18 items) – Green	Adult [46], adulticide [13], aedes albopictus [93], albopictus [63], dengue vectors aedes [14], f1534c kdr mutation [14], female [47], fenitrothion [10], larvae [82], malathion [59], metabolic resistence [15], monooxygenase [10], organophosphate [31], outbreak [56], stegomyia [17], temepho [33], temephos [38], vector population [15].	Identification of kdr at allele f1534c in temephos-exposed *Aedes aegypti* and *Aedes albopictus* mosquitoes
Cluster 3 (12 items) – Blue	Aegypty mosquito [20], bali [21], dengue fever [26], denpasar [21], egg [19], human [15], indonesia [307], jakarta [18], resistance development [28], resistance phenotype [18], surveillance [22], v1016g mutation [14]	Mutation analysis of the v1016g allele in dengue fever-causing mosquitoes in Denpasar, Bali and Jakarta
Cluster 4 (12 items) – Yellow	*Aedes aegypti* mosquito [31], central java [10], channel [130], cypermetrin [14], dengue vector aedes [12], haplotype [43], ile1016 [10], 1982w [13], s989p [46], vgsc [82], vgsc gene [21], voltage gated sodium channel [15]	Identification of kdr in voltage gated sodium channel (VGSC) of *Aedes aegypti* mosquito
Cluster 5 (11 items) – purple	Genotyping [34], insecticide use [13], resistance allele [12], s996 [10], southeast asia [15], target site resistance [10], v1023g [15], voltage sensitive sodium channel [17], vssc [24], vssc muattion [11], yogyakarta [2]	Analysis of voltage sensitive sodium channel (VSSC) in mosquitoes in Yogyakarta
Cluster 6 (9 items) - sky-blue	*Aedes aegypti* [10], aegypti strain [12], chikv [11], dengue virus [23], denv [19], primary vector [18], virus [56], zika virus [24], zikv [18]	Kdr surveillance in the Aedes genus in Indonesia

Information: [N]: the value of terms used together with a number of N values.

4.4 Overlay Visualization

The application of overlay visualization facilitated the illustration of the trajectories of the investigated terms and their employment as research subjects. The results revealed that the progression of the terms from 2018 to 2020 continued to change and expand, with ongoing

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accounts and apprehensions about the occurrence of kdr in Aedes species and genera within Indonesia. The identification results showed the terms "female" (n = 47; link = 52; and total link strength = 251), "primary vector" (n = 18; link = 44; and total link strength = 155), "monooxygenase" (n = 10; link = 28; and total link strength = 68), "voltage sensitive sodium channel" (n = 17; link = 27; and total link strength = 96), "vgsc" (n = 82; link = 60; and total link strength = 456), "f1534c kdr mutation" (n = 14; link = 36; and total link strength = 120), "resistance ratio" (n = 24; link = 47; and total link strength = 172), "pirimiphos methyl" (n = 10; link = 22; and total link strength = 61), "mosquito coil" (n = 19; link = 22; and total link strength = 65), "repellency" (n = 30; link = 22; and total link strength = 130) and "l982w" (n = 13; link = 7; and total link strength = 43) become terms or ocurance that are trending in the current discussion, while the phrase "Indonesia" (n = 307; link = 70; and total link strength = 793), "channel" (n = 130; link = 73; and total link strength = 649), "knockdown" (n = 123; link = 51; and total link strength = 217) and "*Aedes albopictus*" (n = 93; link = 56; and total link strength = 320) became the most dominant and frequently appearing phrases in publications from 2018 - 2020. The data depicted in Figure 3 indicate a high and widespread incidence of kdr in the Indonesian region, although the frequency of occurrence tends to be low. Additionally, reports of insecticide resistance at the international level are relatively rare. It is crucial to obtain information about insecticide resistance at the international level to provide policymakers with "warning" and/or relevant information regarding current mosquito control problems. The use of synthetic chemicals, nonstandardized natural ingredients, or other methods that exacerbate this issue can make it challenging to control mosquito populations.

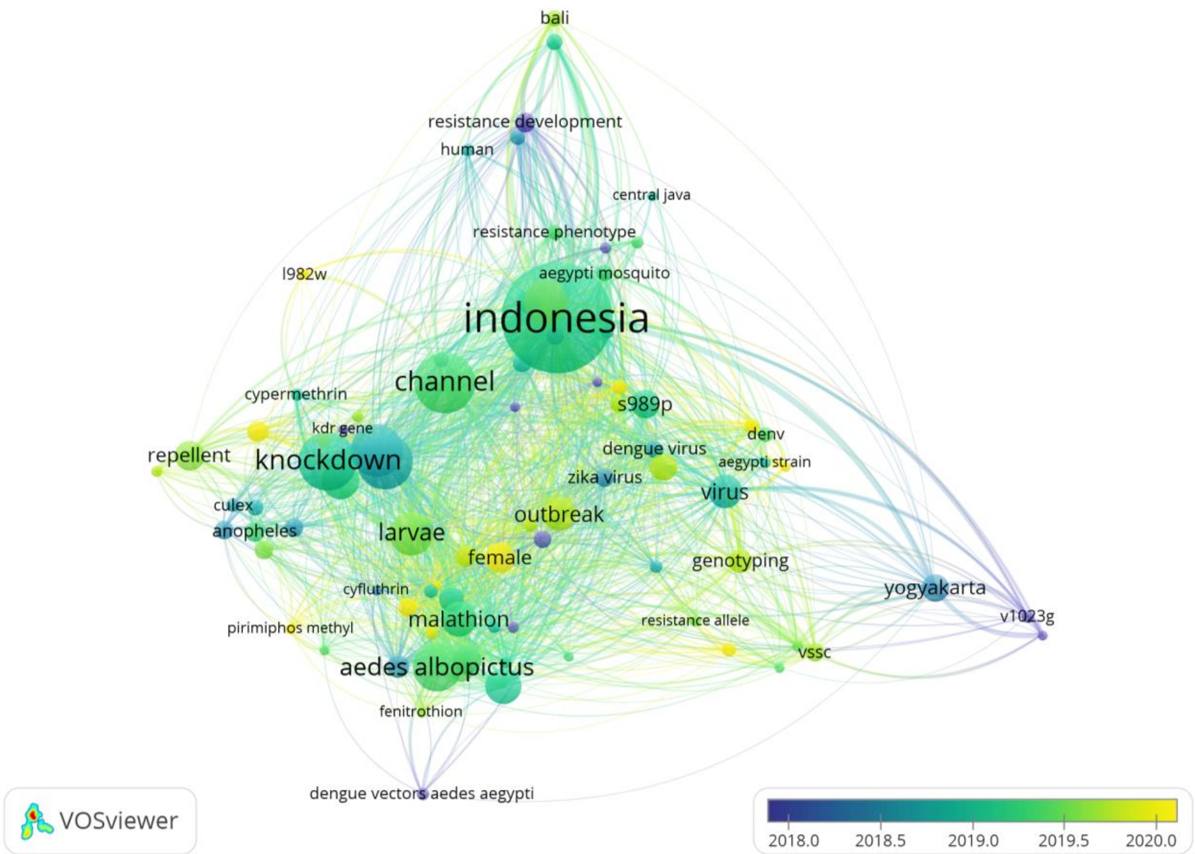

Figure 3. Overlay visualization of terms in each cluster (2018–2020) related to kdr in Indonesia. Darker colors indicate that phrases and/or terms have been researched in the past, while brighter to yellow colors indicate the development of newer term usage. Thicker nodes and lines indicate greater co-occurrence frequencies and stronger relationships, whereas smaller nodes and lines indicate weaker relationships and lower co-occurrence frequencies.

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4.5 Density Visualization

Density visualization was employed to map the depth of each term used in a previous study. The analysis of 14 articles indicated that phrases such as "Indonesia," "channel," "knockdown," "*Aedes albopictus*," "malathion," "anopheles," and "repellent" have been widely researched and formed the focus of previous studies. The total link strength of each phrase was greater than 200, with an average link strength of 45, suggesting that these topics and/or phrases were discussed in 14 publications. The lighter to yellow shaded nodes in each term signify a higher frequency of occurrence and research, whereas the darker or colorless nodes indicate that the phrase has not been widely researched. Moreover, there are considerable opportunities for further research on the identification and surveillance of kdr reports in Indonesia, particularly at the regional, provincial, and district levels. The least frequently occurring phrases, including 'l982w,' 'cypermethrin,' 'target site resistance,' 'pirimiphos methyl,' 'resistance allele,' 'vssc,' 's996p,' 'deet,' and 'iperobyl butpxide,', are likely candidates for additional research on kdr in Indonesia. Density visualizations based on co-occurrence and clustering are shown in Figure 4.

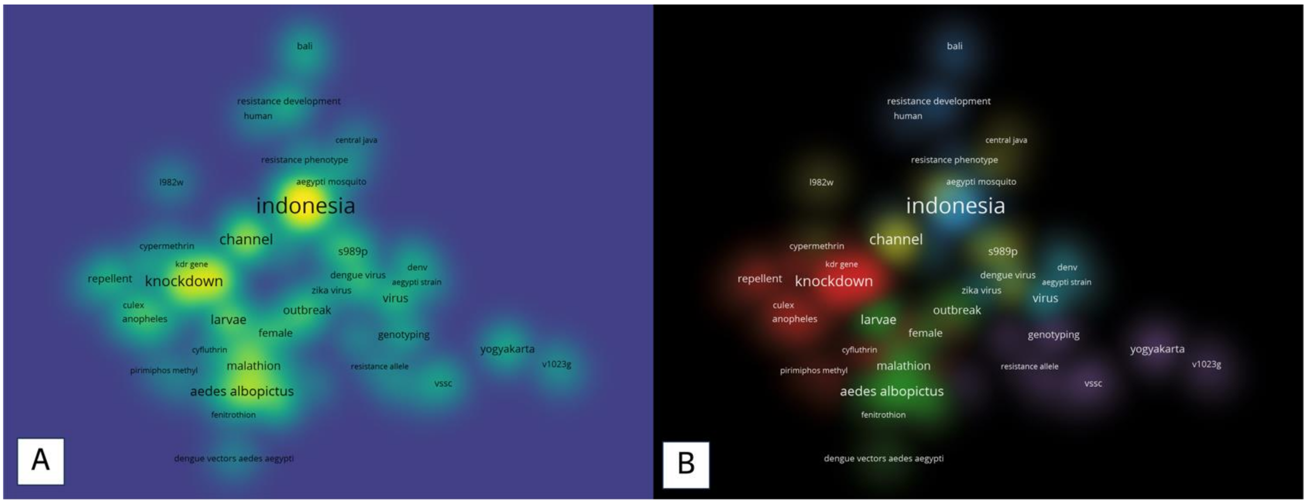

Figure 4. Density visualization based on co-occurrence (A) and clustering (B).

4.6 Hotspots and coldspots of kdr-related research in Indonesia

The identification of hotspot and coldspot areas based on term mapping results is crucial for determining the focus of related research and that has yet to be conducted. These findings indicate that terms with high network strength and a collection of nodes that are far apart should be considered in future research. The identification of kdr in the Aedes genus in Indonesia focused on the 'voltage-gated sodium channel' OR 'vgsc, ʼʼ larvae,' and 'larvae," temephos,' and 'temephos,' which are research hotspots that have high linkage of terms with other terms (Figure 5 A1-A3), while the phrases 'voltage sensitive sodium channel' OR 'vssc,' 'primary vector,' and 'genotyping' became research coldspots characterized by links dominated by recent research on lighter colors and distant nodes (Figure 5 B1-B3). The terms "coldspots" are the main focus areas for future research.

4.7 Publication related to kdr in the genus Aedes in Indonesia

Fourteen articles were collected from Indonesian publications on the kdr gene in the Aedes genus, with an average of 56.67 citations per year. Additionally, the highest number of citations for a single article was 68, whereas the lowest was one. The top 14 publications related to kdr in the Aedes genus in Indonesia are presented in Table 2.

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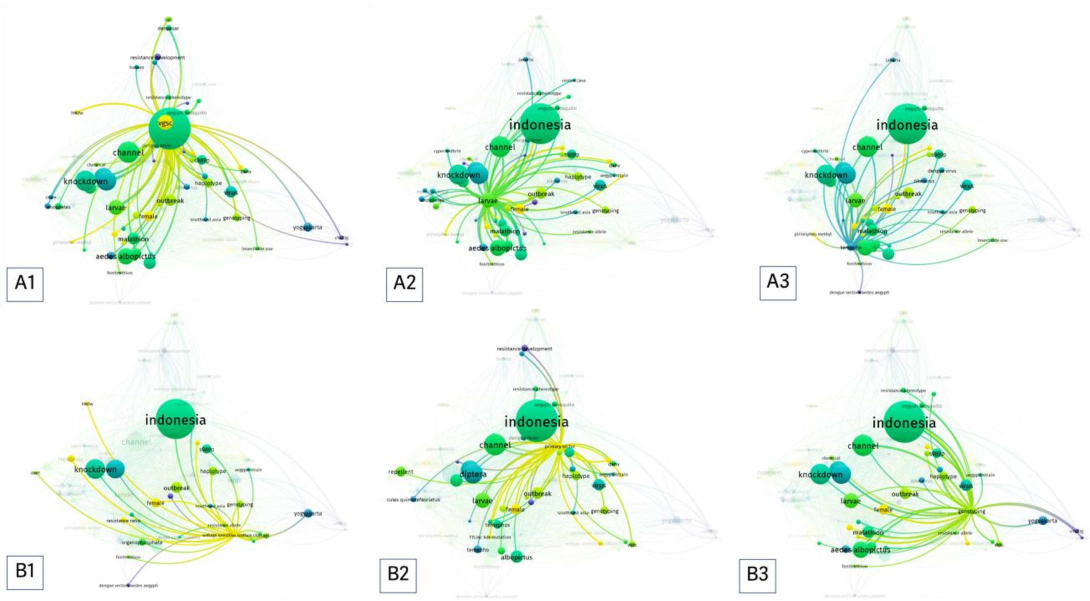

Figure 5. Research on hot spots and cold spots related to kdr in the Aedes genus in Indonesia.

Table 2. Top 14 publications related to kdr in the Aedes genus in Indonesia

Cites	Ref.	Title	CY
68	[10]	Association between Three Mutations, F1565C, V1023G and S996P, in the Voltage-Sensitive Sodium Channel Gene and Knockdown Resistance in *Aedes aegypti* from Yogyakarta, Indonesia.	56.67
68	[14]	Frequency of kdr mutations in the voltage-sensitive sodium channel (VSSC) gene in *Aedes aegypti* from Yogyakarta and implications for Wolbachia-infected mosquito trials.	56.67
52	[11]	The V1016G mutation of the voltage-gated sodium channel (VGSC) gene contributes to the insecticide resistance of *Aedes aegypti* from Makassar, Indonesia	43.33
40	[15]	Knockdown resistance (kdr) of the voltage-gated sodium channel gene of *Aedes aegypti* population in Denpasar, Bali, Indonesia.	33.33
36	[16]	*Aedes aegypti* resistance development to commonly used insecticides in Jakarta, Indonesia.	30.00
35	[13]	Current Status of *Aedes aegypti* Insecticide Resistance Development from Banjarmasin, Kalimantan, Indonesia	29.17
25	[12]	Insecticide resistance in *Aedes aegypti*: An impact from human urbanization?	20.83
12	[19]	V1016G Point Mutation: The Key Mutation in the Voltage Gated Sodium Channel (VGSC) Gene of Pyrethroid Resistant *Aedes aegypti* (Diptera: Culicidae) in Indonesia	10.00
4	[20]	Genotyping of kdr allele in insecticide resistant-aedes aegypti populations from West Sumatra, Indonesia	3.33
2	[21]	Detection of polymorphism on voltage-gated sodium channel gene of indonesian aedes Aegypti associated with resistance to Pyrethroids	1.67
1	[9]	Distribution of Voltage-Gated Sodium Channel (Nav) Alleles among the *Aedes aegypti* Populations in Central Java Province and Its Association with Resistance to Pyrethroid Insecticides.	0.83
1	[22]	Detection of Knockdown-resistance Mutations (V1016G and F1534C) in Dengue Vector from Urban Park, Surabaya, Indonesia	0.83
0	[23]	Detection of homozygous wildtype V1016V using allele-specific polymerase chain reaction in *Aedes albopictus*	0.00
0	[24]	Bioassay and molecular detection of insecticides resistance of *Aedes aegypti*, vector of dengue in Central Java Province, Indonesia	0.00

Information: CY = citations per year.

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5. Discussion

In recent years, mosquito-borne diseases have emerged as a significant threat to public health worldwide, including in Indonesia [4]. The increase in the incidence of these diseases has been attributed to favorable climatic and resource conditions [25–28]. This increasing trend has raised concerns for policymakers, particularly in light of reports on knockdown resistance (kdr) in certain parts of Indonesia. Despite the prevalence of kdr in some regions, the underlying factors contributing to its development have not been fully studied, and limited information is available on its prevalence in different regions. Therefore, understanding the trends and key aspects of resistance in the Aedes genus is crucial for designing effective and efficient disease management and control strategies.

This study focused on Indonesia, with Jakarta, Bali (Denpasar), and Central Java (Yogyakarta) as areas where knockdown resistance was reported. Research has focused primarily on several mosquito species, including *Aedes aegypti* and *Aedes albopictus*, which are the species most closely related to humans. Furthermore, the most studied kdr is related to voltage-gated sodium channels (VGSC) and is currently being expanded to include voltage-sensitive sodium channels (VSSC). The most commonly reported alleles and/or codons associated with resistance in the Aedes genus in Indonesia include c1534, f1534c, ile1016, 1982w, s989p, s996, and v1023g. Kdr has mostly been tested on larvae and eggs and less so on adult mosquitoes. Although allelic variation was not clearly observed in this study, manual inspection of the articles revealed information related to wild-type, heterozygous, and homozygous alleles.

Bibliometric analysis confirmed the spatial distribution of reports of insecticide, larvicide, and adulticide resistance in the community. These findings indicate that long-term use of temephos is associated with an increased ability of mosquito larvae to survive resistance. This finding is in accordance with previous research conducted in Cameroon, Taiwan and China [29–32]. A number of studies have also reported that the use of DEET, malathion, deltamethrin, permethrin, sihalotrin, bediocarb, siflutrin and other agents has contributed to the increased incidence of larval and mosquito resistance to insecticides [11–14,19]. This has become a new obstacle for mosquito-based disease control in Indonesia [21,33,34]. Furthermore, research trends and key findings point to increasing interest in resistance research in the Aedes genus in Indonesia. Over the past decade, there has been a steady increase in publications indicating growing scientific interest and a focus on understanding the resistance mechanisms of these mosquitoes [35,36].

The findings of the bibliometric analysis revealed four key lessons and insights gained from the study. First, most studies in Indonesia have focused on investigating the mechanisms underlying resistance in the Aedes genus, with an emphasis on insecticide resistance and immune responses in Aedes mosquitoes. These studies explored the genetic, biochemical, and physiological factors contributing to resistance and identified potential targets for future mosquito-borne disease control strategies based on the focus of resistance [37–39]. Second, vector control strategies aimed at controlling mosquito-borne diseases, particularly those caused by the genus Aedes, have been the primary focus of related research. Alternative approaches to conventional insecticides, such as biological control methods, Wolbachia-based interventions, and new mosquito repellents, will continue to evolve and be further investigated [4,25,40]. Third, it is crucial to consider geographical variation when designing region-specific interventions, considering local cultures, customs, and habits. Fourth, collaborative efforts involving multidisciplinary collaborations among entomologists, epidemiologists, molecular biologists, and public health experts have emerged as key themes in research, emphasizing the importance of a comprehensive approach to address kdr in the Aedes genus in Indonesia [41–44].

Efforts have been made to reduce the prevalence of resistance in the Aedes genus, especially in Indonesia; however, information from this surveillance suggests that the use of focal fogging, insecticides, synthetic larvicides, spray and burn mosquito repellents, and other agents has contributed to the incidence of resistance [43–45]. Excessive and indiscriminate use of insecticides, particularly pyrethroids, is a predisposing factor. The continuous exposure of mosquitoes to these chemicals has resulted in the establishment of repellent-resistant populations. Furthermore, the inadequate implementation of integrated vector management (IVM)

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strategies, such as relying solely on a single method, such as insecticide fogging, without rotating or combining it with other control measures, promotes the development of more extensive resistance [46,47]. The inconsistency or incomplete adherence to prescribed doses and methods of insecticide application by professionals and the general public also contributes to the development of resistance, leading to more aggressive mosquitoes and increased morbidity and mortality [48–50].

The lack of monitoring and surveillance systems for detecting resistance patterns and mosquito population trends hinders timely intervention and adaptation of control strategies [51,52]. Constraints on human, financial, and manpower resources limit the scope of routine surveillance [53,54]. Additionally, mosquito populations exhibit natural genetic variability that can lead to mutations that predispose certain individuals to insecticide exposure. Over time, these individuals pass on resistance traits to their offspring, contributing to the rise of resistant populations [55–57]. These phenomena are influenced by physical and environmental factors that are undergoing significant transformations, as well as human activities, such as urbanization and the international spread of resistance. Therefore, it is essential to implement a comprehensive health strategy to maintain control over these predispositions [58–60].

5.1 Limitations and Novelty

This study concentrates specifically on the dissemination and reported frequency of knockdown resistance within the Aedes genus in Indonesia, encompassing provinces and/or districts. Unfortunately, the limited scope of information available in the Scopus database restricts the generalizability of our conclusions. The global frequency of kdr resistance reports in Indonesia is relatively low, which makes this information valuable for future research. However, this study did not provide a comprehensive examination of the percentage of kdr incidence in each region, necessitating further analysis, such as systematic reviews and meta-analyses.

6 Conclusion

There has been a significant increase in the incidence of kdr in the genus Aedes in Indonesia. Bibliometric analysis was used to explain the growth trend, identify current research hotspots and coldspots, and make recommendations for future research. This study showed that the incidence of kdr in the genus Aedes was reported in 2018. Based on network visualization, 86 terms corresponding to this research topic were generated, resulting in at least six main clusters and 1,496 links, with a total link strength of 7,188. Of the 14 articles analyzed, the mosquito species of the Aedes genus that were reported to be resistant were *Aedes albopictus* and *Aedes aegypti*. The types of insecticides reported and suspected to cause kdr are pirimiphos methyl, cyfluthrin, piperonyl butoxide, cyhalothrin, cypermermethrin, transflutrin, temephos, malathion, organophosphates and fenitrothion. For the intended kdr target, the alleles affected under these conditions were f1534c, l982w, s989p, v1023g, and s996p. The regions, provinces, and/or districts in Indonesia with the most reported kdr reports in the Aedes genus are Yogyakarta, followed by central Java, Bali, Denpasar, and Jakarta. Based on these findings, we highlight that only provinces classified as large cities report the incidence of kdr at the international level, whereas other regions may be reported, but only on a national scale. This highlights the importance of focusing on understanding resistance mechanisms, exploring new control strategies, addressing geographic variation, and encouraging collaborative efforts to underscore the importance of a comprehensive approach to combating mosquito-borne diseases. This surveillance provides valuable insights for policymakers, researchers, and public health practitioners for formulating targeted interventions to mitigate the future impact of Aedes mosquito-borne diseases in Indonesia.

7. Declaration

Ethics approval: This study has been approved and registered in the PROSPERO database under the number CRD42023465281.

Acknowledgments: We thank PT Mega Science Indonesia for assisting with the translation, editing, and proofreading of the manuscript so that it is suitable for publication.

Conflict of interest: The authors declare that they have no conflicts of interest.

Funding: This research did not receive funding from any party.

Underlying data: All the data underlying the results are available as part of the article, and no additional source data are needed.

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