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Review article

Monitoring of synthetic insecticides resistance and mechanisms among malaria vector mosquitoes in Iran: A systematic review

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ABSTRACT

Background: In Iran, the prospect of malaria control relies mainly on insecticides used against the genus *Anopheles* (Diptera: Culicidae) as important vectors of malaria, arboviruses, and so on. Only eight out of 30 malaria mosquito vectors (*Anopheles* species) have been examined for insecticide resistance in Iran. This study aimed to review articles related to the incremental trend in insecticide resistance and their mechanisms among anopheline malaria vectors in Iran.

Methods: A literature review was conducted based on such search engines as Iran doc, Web of Science, SID, PubMed, Scopus, and Google Scholar websites using the following keywords: "*Anopheles*," "Malaria," "Resistance," "Vectors," "Insecticide Resistance," and "Iran" for data collection. Published papers in English or Persian covering 1980 to 2020 were reviewed.

Results: A total of 1125 articles were screened, only 16 of which were filtered to be pertinent in this review. While most of the mosquito vectors of malaria, such as *Anopheles stephensi,* were resistant to DDT, dieldrin, malathion, and becoming less susceptible to deltamethrin and other synthetic pyrethroid insecticides, few like *Anopheles fluviatilis* s. l. were susceptible to all insecticides. A disseminating trend in insecticide resistance among different anopheline mosquito vector species was evident. Metabolic and insecticide target-site resistance mechanisms were involved with organochlorines and pyrethroids, respectively.

Conclusions: Insecticide resistance is becoming a severe scourge to the effectiveness of vector-borne disease management measures. This event is especially critical in developing and marginalized communities that applied chemical-based vector elimination programs for malaria; therefore, it is crucial to monitor insecticide resistance in malaria vectors in Iran using biochemical and molecular tools.

1. Introduction

Vector-borne diseases responsible for 17% of all cosmopolitan infections are considered significant global public health problems leading to the tremendous economic burden imposed on affected societies by insidious pathogens. The emergence and re-emergence of these diseases in the last 40 years have mainly been driven by population growth, urbanization, globalization, and lack of public health infrastructure [1]. Arthropods generate diseases mostly in tropical and subtropical regions [2] and excessively influence the poorest populations in the middle- and low-income countries [3]. Chikungunya, dengue, rift valley fever, yellow fever, and Zika are expressed as common viral diseases transferred by mosquitoes in different regions within human populations [4, 5]. Consequently, various disease overlaps occur as they share common vectors. Since the geographical disease distribution patterns are related to these poikilothermic vectors [1], co-infection or co-occurrence of more than one disease is quite common in a specific region [6].

Pathogen transmission prevention is a crucial factor of disease management to reduce human morbidity and mortality, and economic losses due to illness. Vector population suppression is suggested as one of the main breakthroughs to inhibit disease transmission through chemical- and non-chemical methods [1]. Vector control was programmed for

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decades mainly through insecticide use against mosquito larvae and adults, leading to the rise of insecticide resistance on targeted insect populations [7, 8].

Malaria is one of the most critical vector-borne parasitic diseases in Iran. It is a significant cause of morbidity and mortality, and about half of the world population is predisposed to this infection [9, 10]. Malaria disease is caused by the *Plasmodium* Marchiafava & Celli, 1885 (Apicomplexa, Plasmodiidae) parasite through infectious bites of female *Anopheles* Meigen, 1818 (Diptera, Culicidae) mosquitoes. Nowadays, it is mainly restricted to the Oriental region of Iran [11].

Although it has traditionally been endemic over much of the Persian Palearctic plateau, instigating an early malaria eradication campaign from the fringes of its transmission range with strict reliance on indoor residual spraying since last century [12], its incidence has recently declined "from 0.24/1000 in 2002 to 0.01/1000 in 2017" [13], mainly in the three southeast Hormozgan, Sistan-Baluchistan, and Kerman provinces (Figure 1) [14]. In Iran, malaria is unstable, with a stability index of less than 0.5, which is the "average number of bites by an average mosquito during a normal lifetime" [15]. Iran has thus embarked on a malaria elimination plan in 2009 with a target to get its certification by 2025 [13].

The national Iranian key control prevention policies and strategies implicate four dominant interventions: indoor spraying of surfaces, free dissemination of insecticide-impregnated bed nets to all households, free malaria diagnosis, active or passive case recognition, and disease treatment, and eventually source reduction of larval mosquito ecosystem [11]. Given these control policies, Iran succeeded in a strategic plan to achieve the 2020 goal of zero autochthonous malaria transmission and has thus eliminated this disease early last year [16].

By and large, 30–34 different species of *Anopheles* have been identified by morphological and molecular phylogenetic analyses; only eight species are incriminated as definite vectors of malaria [17, 18], which are the subject matter of this article. Mechanical vector control methods such as source reduction and bed nets had long been instrumental as practical ways to curb this disease from the 1900s to 1960 [19,20]. On the other hand, chemical insecticides have likewise been used as medicinal plants and sulfur-contained insecticides [21]. In the 19th century, pyrethrum was introduced as a botanical pesticide [22]. Dichlorodiphenyl trichloro-ethane (DDT) was applied as a dominant insecticide in the USA until 1975, when organophosphates and carbamates were replaced. After that, pyrethrin compounds have frequently been implemented [23].

Figure 1. A country map of Iran and its provinces within this region.

Vector-borne disease (VBD) elimination program has been unsuccessful due to disparate ecosystems in all parts of Iran. Insecticide-based strategies are the key intervention and support of VBD control efforts. One of the most important reasons for the failure of the VBD elimination program has inevitably been the resistance of vectors to the most frequently used insecticides [24].

The primary malaria vector, *Anopheles stephensi* Liston, 1901 is resistant to DDT, dieldrin, and malathion, and synthetic pyrethroids appear to have faded their efficacies against vectors in most parts of southern Iran [25, 26]. Two different metabolic and target-site insensitivity mechanisms are involved in insecticide resistance [27]. Studies from malaria-prone areas have indicated that resistance to be confirmed (RC) and susceptibility of *A. stephensi* to deltamethrin and permethrin insecticides have respectively been proven [28]. Permethrin is stated to eliminate many vectors, including those of malaria parasites.

Following an earlier review article in a Persian journal in 2016 [29], it seemed plausible to recapitulate this thematic issue once again due to the sensitivity and gravity for public health concerns in this regard [30]. The present systematic review outlined significant investigations in the last 40 years in synthetic insecticide use against malaria vectors in different parts of Iran.

2. Methods

The protocol of the current study was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [31]. Since this study was a systematic review of published articles, there is no need for patient consent or institutional ethics committee approval. The standard WHO 2016 criteria for resistance status were followed as 98–100% mortality being labeled as susceptible; 90–97% mortality being possible resistance or resistance to be confirmed; and <90% mortality being resistant [32].

2.1. Eligibility criteria

A prior delimitation of eligible literature exhibiting pre-determined specifications for inclusion-exclusion criteria is outlined in Table 1. A clearly-formulated question is: What are the updates on "Monitoring of synthetic insecticides resistance and mechanisms among malaria vector mosquitoes in Iran?" All limitations, inconsistencies, and heterogeneities are embodied.

Table 1. Eligibility criteria for literature review on insecticide resistance of malaria vectors in Iran.

Attributes	Inclusion criteria	Exclusion criteria
Date	April 1980 to March 2020	Pre-1980 publications
Geography	Iran	Non-Iranian territories
Exposure of interest	- All 8 malaria vectors (Table 3) - Insecticide classes: OC, OP, C, & PY - 2 or 4 insecticides from each class	- Non-vector malaria mosquitoes - Other insecticide classes, *e.g.* IGRs
Participants	- Adult malaria mosquitoes - WHO modules and dosages	- Immature mosquito stages - Non-compliant formulations
Language	English, Iranian	Foreign manuscripts
Peer review	Peer-reviewed literature	Grey and non-peer-reviewed articles
Outcome	Consistent WHO-based manner	Self-declared bypassing objective measures
Settings	Laboratory- or field-based	Self-devised improper settings
Study design	Experimental, analytical	Descriptive, observational
Study type	Original papers	Reviews, editorials, letters

OC, organochlorines; OP, organophosphates; C, carbamates; PY, pyrethroids; IGRs, insect growth regulators; WHO, world health organization.

2.2. Search strategy

Following a procedure of database search including: Web of Science, PubMed, Scopus, Medline, Iran doc, and Google Scholar. All searches were updated to 2020 (Figure 2). The terms used for research were included: "*Anopheles*," "Malaria," "Resistance," "Vectors," "Insecticide Resistance," and "Iran." In addition, references of previous review articles were noticed for valuable articles.

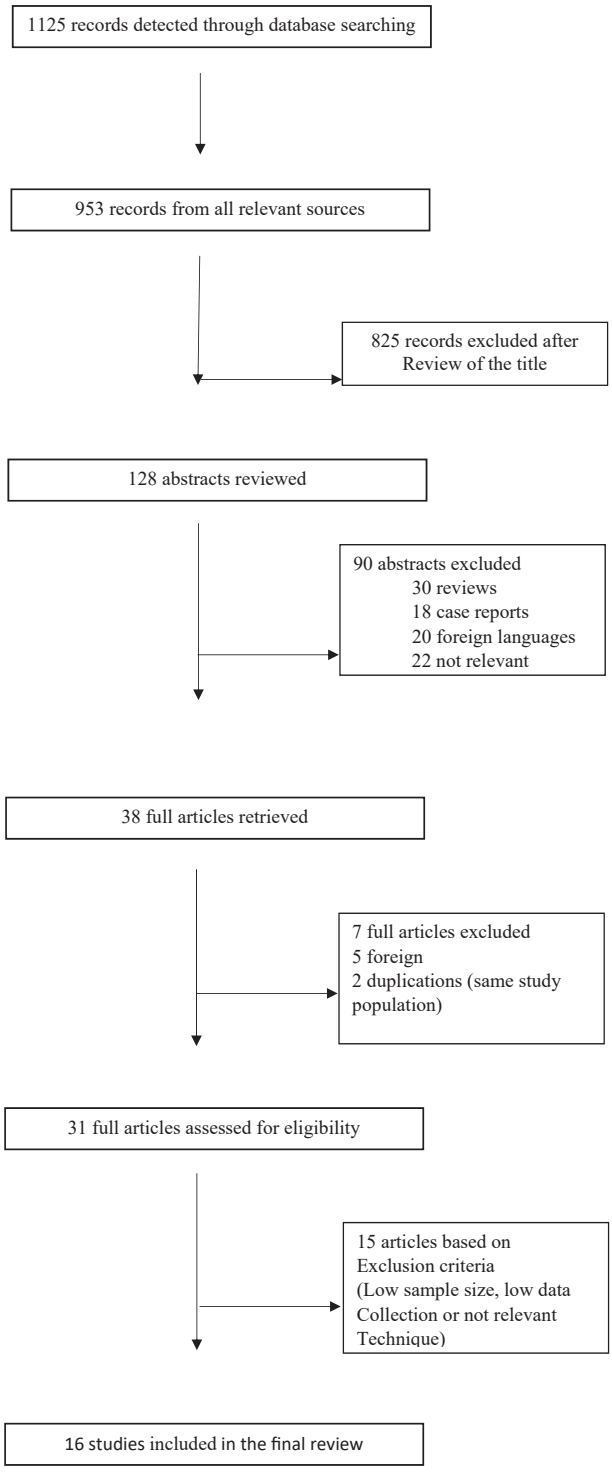

Figure 2. Flowchart diagram or PRISMA flow diagram of studies included in this review.

2.3. Study selection

Three authors independently evaluated all the titles and abstracts to detect pertinent studies matching the inclusion criteria. Discrepancies on inclusion and exclusion criteria were resolved by a consensus meeting where two additional reviewers were enrolled. Finally, 16 studies were eligible for analysis, but no meta-analysis on collected studies was performed due to the lack of a dichotomous answer to a proposed binary question. We identified some studies as highly heterogeneous but did not exclude any of them for low quality (STROBE checklist)—evaluation of the risk of bias of individual studies identified as potential sampling bias. The substantial heterogeneity and recognized risk of bias across and within studies did not allow for pooled estimates or meta-analysis of variables. However, the main characteristics of individual studies were listed. We neglected the risk of bias of individual papers.

3. Results

3.1. Literature

A total of 1125 articles were retrieved and screened, only 16 of which were finally filtered to be pertinent for this review (Figure 2). About 9% (128 papers) of the original search were scrutinized for conformity to our inclusion criteria. Only 38 full articles were selected, from which 22 were dropped out due to various exclusion factors such as low sample size.

3.2. Rostrum

Details of ten insecticides commonly used to control insect vectors, their chronological replacements, and their resistance mechanisms in Iran are summarized in Table 2. Different malaria vector species have become resistant to various insecticides, causing severe problems in eliminating malaria, particularly in the Oriental regions of Iran. The hierarchy of resistance was initiated with organochlorine insecticides followed by organophosphate, carbamates and terminated with synthetic pyrethroids (Table 3). Due to the restricted diversity in the modes of action of insecticides, the challenge of cross-resistance could not be ruled out. The prospect of elucidating resistance mechanisms often remained bleak in various early publications. As can be discerned from Table 3, sustained vigilant monitoring of a few critical malaria vectors, such as *A. stephensi, A. sacharovi,* and *A. culicifacies* s. l. Giles, 1901 is well-guarded, whereas specific gaps in research on other vectors (*e.g., Anopheles pulcherrimus*) remain to be investigated.

3.3. Insecticides

One of the first used insecticides against *Anopheles* in the malaria elimination program was DDT, which still influences particular species of mosquitoes. The phenomenon of insecticide resistance began in late 1957, the same year as the beginning of the malaria eradication program, with the emergence of resistance due to indoor residual spraying with DDT in southern regions of the country. Subsequent studies from 1950 to 1987 showed that this resistance to DDT has been due to the rise in the glutathione-S-transferase (GST) enzyme activity [33, 34]. There is doubtless resistance of most anopheline mosquitoes to organochlorines, except for *A. fluviatilis* s. l. James, 1902 and *A. pulcherrimus* Theobald, 1902.

The rise of DDT resistance led to the persistence of the malaria epidemic in some southern parts of Iran, such as the townships of Bandar-Lengeh and Bandar-Abbas, persuading both Iranian and WHO experts to replace it with dieldrin (Figure 1). Two years after the use of dieldrin, in 1960, cases of resistance to dieldrin were observed in the spraying areas with this insecticide, and *Anopheles* (*e.g., A. maculipennis* s. l. Meigen, 1818) also showed resistance to dieldrin [35, 36]. The mechanism of resistance to dieldrin has been an alteration in gamma-aminobutyric acid receptors in the neuronal endplates of *A. stephensi* [33]. Between 1961 and 1966, the malaria control program focused on insecticide spraying in DDT-sensitive areas and other control measures and patient treatments in refractory areas [33]. There was thus an increasing phase of resistance to these organochlorines [37, 38, 39] in the 1970s, followed by a gradual falling phase [40, 41], likely due to the prohibition of further organochlorine use, in the final two decades of the last century. This shortly-increased susceptibility soon reverted to its dropping status in *A. stephensi* possibly due to the "emergence of resistance to pyrethroid insecticides" [26].

In 1968, malathion-infused indoor spraying was selected as an effective means in these areas, and spraying operations were carried out intermittently using malathion for *A. stephensi*, and DDT for other *Anopheles* species. A substantive outcome was achieved in reducing malaria incidence in these areas [42, 43]. In 1977, malaria resistance was reported where an esterase had been identified as the primary cause and oxidases as additional factors in the development of *Anopheles* resistance to malathion [44].

Following this resistance, indoor spraying with propoxur replaced malathion. The use of propoxur insecticide continued until 1991 in southern regions of the country. This insecticide was thus removed and replaced by lambda-cyhalothrin due to the report of vector resistance to propoxur and a financial advantage [44]. The organophosphates and carbamates have induced partial tolerance or resistance to be confirmed in a few (*i.e.,* two) *Anopheles* species.

Pirimiphos-methyl was subsequently recommended to be used in place of propoxur in 1991. This was also forbidden in favor of lambda-cyhalothrin with propoxur in 1994 [26,44,45]. No cross-resistance has been found between malathion and pirimiphos-methyl in different *A. stephensi* strains of Iran [44].

Table 2. Chronological list of the most commonly used insecticides against malaria vectors in Iran.

#	Insecticide name	Insecticide class	Year of use*	Year of resistance	Replaced insecticide	Mechanisms of resistance	Ref.
1	DDT	OC	1945	1957	Dieldrin	GSTs	[51]
2	Dieldrin	OC	1958	1960	Malathion	aGABA-R	[33]
3	Malathion	OP	1968	1977	Propoxur	GSTs, aAChE, ESTs	[84, 85]
4	Propoxur	C	1978	1991	λ-Cyhalothrin	-	[44]
5	Pirimiphos-methyl	OP	1991	1994	λ-Cyhalothrin	aAChE	[26]
6	Bendiocarb	C	1978	-	λ-Cyhalothrin	ESTs	[47]
7	λ-Cyhalothrin	PY	1994	2003	Deltamethrin	P450s	[47, 56]
8	Deltamethrin	PY	2003	2011	-	P450s	[47, 86]
9	Permethrin	PY	-	-	-	P450s	[47, 87]
10	Cyfluthrin	PY	-	-	-	P450s, GSTs	[71]

* Abai et al. [88]; OC: Organochlorines; OP: Organophosphates; C: Carbamates; PY: Pyrethroids; GSTs: Glutathione S-transferases; aGABA-R: Altered gamma-aminobutyric acid receptor; aAChE: Altered acetylcholinesterase; ESTs: Esterases; P450s: microsomal P450 monooxygenases (mixed-function oxidases, MFO).

Table 3. The outcome of different malaria *Anopheles* vector species susceptibility/resistance to Iran's most frequently used insecticides. Numbers insert new references within square brackets [29].

Species	DDT	Dieldrin	Malathion	Bendiocarb	Propoxur	Deltamethrin	Cyfluthrin	λ-Cyhalothrin	Permethrin
A. stephensi	R [89, 90]	R [89]	R [28]	R [47]	S	RC [28]	R [28]	R [28]	S [28]
A. maculipennis	R	R [52]	R [51]	R [48]	R [48]	RC	NR	S [52]	RC [48]
A. sacharovi	R [53]	RC [53]	S	S [63]	S [63]	R [54]	S [63]	S [63]	S [63]
A. dthali	R	S	RC	NR	NR	RC	NR	NR	NR
A. culicifacies	R	R [46]	R [91]	RC [46]	RC [46]	RC [46, 54]	RC	S [29]	S [29]
A. fluviatilis	S	S	S	NR	NR	S	NR	NR	NR
A. superpictus	R [56]	S	S	NR	NR	S	NR	S [56]	NR
A. pulcherrimus	NR	NR	NR	NR	NR	NR	NR	NR	NR

R: resistant; S: susceptible; RC: resistance to be confirmed; NR: not reported.

Indoor residual spraying with bendiocarb, which started simultaneously in 1978 as that for propoxur, was used in subsequent years mostly in malaria-prone Oriental parts of Iran. One study reported female *A. culicifacies* s. l. partial resistance to bendiocarb and propoxur in Sistan-Baluchistan province monitoring [46]. Thus, bendiocarb was later replaced with lambda-cyhalothrin in this region, while esterases were involved in malaria vector resistance to this carbamate [47].

After nine years, deltamethrin replaced lambda-cyhalothrin in 2003 [34]. Malaria vectors' resistance occurred apace, and in some cases, even deltamethrin could seldom be used in malaria eradication. Permethrin resistance for malaria vectors in Iran is unreported, although one report of resistance to be confirmed in *A. maculipennis* s. l. from northwest Iran is documented [48].

3.4. Mechanisms of resistance

Insecticide resistance mechanisms included GSTs, cytochrome p450s, and gamma amino-butyric acid-receptor change for organochlorines. Altered acetylcholine esterase and other esterases, cytochrome p450s, and GST were implicated in resistance to synthetic pyrethroids, bendiocarb, and malathion. More than one mechanism may be involved in certain instances. Including a specific mechanism in two different insecticides classes could give cross-reactivity. It is noteworthy that the metabolic mechanism is the most investigated in these studies.

3.5. Malaria mosquito vectors

Among eight incriminated anopheline mosquitoes of malaria, *A. stephensi* is the primary vector whose role and mechanisms in insecticide resistance in the WHO Eastern Mediterranean region, including Iran, was thoroughly reviewed very recently [26]. This review showed how the evolution of insecticide resistance in this urban mosquito vector could tackle malaria elimination both regionally and the lands beyond.

The second primary malaria vector is *A. culicifacies* s. l., which is a species complex with five siblings in the Oriental region of Iran extending across Pakistan into sub-continental India. It has been found to be resistant to DDT, dieldrin, and malathion while being tolerant (RC) to bendiocarb, propoxur, cyfluthrin, and deltamethrin, but susceptible to other pyrethroid insecticides in Sistan-Baluchistan province [46]. A GSTe2 (Epsilon 2) insecticide resistance gene was not detected in a study on this and two other malaria vectors in this province, *A. culicifacies* s. l. and *A. fluviatilis* s. l. [49], but confirmed in *A. stephensi*. This finding reflects that the underlying molecular mechanism responsible for the regulation of insecticide resistance is poorly known [50].

Another species complex with four siblings is *A. fluviatilis* s. l. whose remote distribution in foothills and flood valleys renders it a more efficient vector than the above two species in lowland semi-arid plains [12]. No report of reduced susceptibility in this malaria vector of the Oriental region of Iran has so far emerged. *A. fluviatilis* s. l. is the only investigated species of malaria vectors being susceptible to all insecticides.

The third species complex is *A. maculipennis* s. l. with 24 siblings whose distribution extends into continental Europe, the Middle East, and North Africa [51]. Only seven of these siblings, including *A. sacharovi* and *A. maculipennis* s. s., are dispersed in 20 Iranian provinces, mainly northwest Iran. It has been found to be susceptible to lambda-cyhalothrin [51, 52] but resistant to DDT, dieldrin, malathion, bendiocarb, and propoxur [48, 51, 52], and possible resistant or tolerant to deltamethrin and permethrin [29, 48]. Its reaction to cyfluthrin remains to be evaluated. Similarly, a GSTe2 gene mutation is responsible for DDT and organophosphate insecticides resistance in this malaria vector [51].

On the other hand, *A. sacharovi* has been reported to be susceptible to most insecticides, except DDT [53] and deltamethrin [54], but resistance to be confirmed for dieldrin [53]. The causative mechanisms for DDT and deltamethrin resistance are GST and cytochrome P450 enzymes.

One of the most widespread malaria vectors is *A. superpictus* s. l. complex with at least three sibling species; X in the Palearctic and Y and Z in the Oriental parts of Iran [55]. This vector has resistance to DDT but is susceptible to dieldrin, malathion, deltamethrin, and lambda-cyhalothrin [56]. Although its mechanism to DDT resistance is not explicitly indicated, a similar GST system is likely to be implicated in this malaria mosquito.

The seventh anopheline is *A. dthali* Patton, 1905 sympatric with the sibling species X of *A. culicifacies* s. l. and a secondary malaria vector with mainly exophilic and zoophagic tendencies, whose resistance to DDT is confirmed. Its partial resistance (RC) to malathion and deltamethrin is reported, while it remains susceptible to dieldrin. The underlying mechanism of resistance to DDT is likely to be GST-based again.

Finally, as to the case of the last malaria vector, *A. pulcherrimus*, prevalent in the coastal provinces of the Persian Gulf, there has been no investigation on it so far. The susceptibility status of *A. pulcherrimus* to different insecticide groups remains to be evaluated in the future.

4. Discussion

Hematophagous arthropods vector various disease agents to companion animals or humans by blood-sucking mosquitoes, ticks, sand flies, fleas, lice, and other biological transmitters of pathogens in vector-borne diseases [57, 58]. One of the best-known mosquito-associated diseases is malaria, which is among the principal causes of worldwide human mortality. As a result of the scale-up of insecticide-treated nets and indoor residual spraying programs despite two operationally contrasting approaches [12], resistance to insecticides has swiftly developed at a high rate throughout much of the malaria-affected regions worldwide [33].

The current monitoring of synthetic insecticides resistance and mechanisms among most malaria vectors demonstrates a successful national vector control program towards disease elimination, particularly in hotspot regions. Iran is on route to eliminating malaria with no autochthonous cases in 2017 and 2018 [16]. Malaria mosquito control is an indispensable prerequisite of lowering transmission.

There is, however, a limited list of chemical insecticide groups [59] with similar mechanisms of action and the emergence of a cross-resistance phenomenon [60]. Resistance itself is naturally a very focal and dynamic trait, which should be borne in mind in any vector-borne disease control program since the natural history of malaria disease exhibits itself as a local clustering event [61]. For instance, malaria has long been ceased from Fars province, and the susceptibility bioassays are somewhat unsupported [26]. Few studies have been conducted on insecticide resistance's national and regional impact, and numerous confounding factors complicate interpreting results from these reports. Comprehensive research studies are thus necessitated to vindicate earlier reports.

Very often, the initial single or double resistance of mosquitoes to organochlorine insecticides such as DDT and dieldrin in specific settings culminates in cross-resistance to a range of pyrethroid insecticides [33]. A cross-resistance gene between different insecticide classes has been identified and validated in the principal malaria vector, *Anopheles gambiae* Giles, 1900 in the African continent [62].

Neither eradication nor elimination aims to exterminate mosquito vectors of malaria [15], somewhat malaria mosquito control and surveillance management is an urgent necessity of reducing transmission. Management of resistance to insecticides has commonly been implemented following the rise of resistance. However, suppose the probability of resistance development to new insecticides could be predicted prior to their application. In that case, it might be possible to design an optimum resistance management strategy that will enable applicators to use these compounds effectively against vector mosquitoes, specifically resistant ones.

Likely, different mosquito vector strains of malaria from the same geographic origin display diverse pyrethroid resistance mechanisms. It could also be discerned that insecticide resistance in a specific mosquito vector population is gradually abated, and susceptibility reverses after insecticide pressure withdrawal [63].

Malaria mosquito vectors have developed resistance to most chemical insecticides in Iran [18]. Moreover, numerous reports have indicated that effective and efficient resistance mechanisms such as over-activity or up-regulation of detoxification enzymes and diminished sensitivity of the target proteins –or target site insensitivity-are mainly and most likely responsible for insecticide resistance [22, 27, 64].

Considering that indoor spraying and insecticide-treated nets are but two major operational strategies in combating malaria disease, as well as the premise that there is an increasing dependence on the application of a single class of insecticides (*i.e.*, the pyrethroids) due to their multiple advantages and their official approval [65]; it is uncertain what will replace the pyrethroid-treated nets if the dominance of multi-resistance mechanisms leads to widespread deletion of this approach [50]. In addition, "what combinations of mechanisms of insecticide resistance produce operationally significant levels of resistance that will affect the different vector control interventions?" [15].

There is no molecular evidence for a *kdr*-like (knock-down resistance or target site insensitivity) pyrethroid resistance mechanism in the malaria vector mosquito, *A. stephensi,* in Iran [50, 66]. No clear-cut evidence of insecticide-treated nets continuing to exert adequate personal protection against malaria in an area with *kdr* target receptor-coding gene mutations present in the vector population exists [67, 68]. Insecticide resistance is considered a significant constraint on vector control through indoor spraying sustainability. The greater the insecticide selection pressure persistence in house spraying operations, the higher the probability resistance would evolve [15]. The knowledge and management of insecticide resistance should be an integral part of vector control programs.

Spatiotemporal discrepancies and climate conditions should be implicated when dealing with reports of insecticide resistance among malaria mosquito vectors [69, 70]. For instance, the data from two recent studies on *A. stephensi* adult mosquitoes from Bandar-Abbas and Chabahar seaports in south Iran found resistance to pyrethroids, carbamates and DDT, and cyfluthrin insecticides, respectively [47, 71].

It is necessary to undertake regular monitoring for insecticide resistance to detect and prevent this event in hot spot regions proactively. If this operational resistance goes unchecked, it can ultimately settle in the mosquito population as preliminary lethal effects on their fitness are mitigated by reparatory mutations. In this scenario, strategies to reconstruct susceptibility in field mosquitoes are highly remote to be efficacious [65].

This review article bodes well to appreciate better the development of insecticide resistance of malaria mosquito vectors in Iran and how to evade or counter them. The screening of valid published papers exhibited a coherent picture of the insecticide susceptibility status of different malaria mosquitoes in this country during the last four decades. However, a few reports showed that the bioassay of insecticide resistance was inconsistent across the surveyed studies.

The lack of molecular markers to assert the presence of alternative resistance mechanisms is a problematical issue in most studies in this field since the availability of *kdr* alleles is often used as a proxy for resistance. This outcome can be elusive if metabolic or other resistance mechanisms are the main processes of resistance. There is an urgent need to perform appropriately controlled trials to evaluate the pyrethroid resistance impact on indoor residual spraying and insecticide-treated nets, solely or synergistically. Furthermore, improving vector and VBD surveillance is essential to implement the best-integrated vector management interventions in the One Health Concept [72].

One of the limitations in this review was its restriction to English and Persian literature, which could have been avoided if a broader range of languages could be contemplated. To sustain a malaria elimination plan in the post-elimination period, knowledge on other important malaria vectors seems indispensable. Since resistance in vectors is naturally inevitable, it is vital to use strategies to delay it or minimize the consequences of resistance.

Chemical intervention does not indispensably have to decapitate vectors to prevent pathogen transmission [22]. Alternative approaches should thus be sought. Many new specific vector control strategies aim either to directly attenuate or even eliminate vector population survival, such as genetic identification and modification of mosquitoes [73, 74], special manipulation of the insect vector species microbiome [75, 76], spatial repellents against infected vector insect [77, 78, 79, 80, 81], eave tubes [82] and using liposomes as *in situ* slow-release nano-carriers to deliver chemicals [83]; or target the natural history of pathogens within their vectors such as the incorporation of anti-pathogenic chemosterilants like pyriproxyfen within insecticide formulations to block pathogen transmission [22].

5. Conclusions

Since the start of its control campaign, the cessation of malaria transmission has infringed on three mainly distinct practical periods chronologically: sanitation, eradication, and elimination [15]. Insecticide resistance is becoming a severe threat to the effectiveness of VBD measures due to the ubiquitous use of pyrethroids in insecticide-treated nets, which is especially critical for countries that follow chemical-based vector elimination programs. Therefore, it is crucial to regularly monitor insecticide resistance in all malaria mosquito vectors in Iran.

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Author contribution statement

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Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

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