Review Article

Monitoring and Mapping of Insecticide Resistance in Medically ImportantMosquitoes (Diptera: Culicidae) in Iran (2000–2020): A Review

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Abstract

Background: Mosquitoes due to their role in the transmission of different pathogens to humans are considered as an important group in the phylum Arthropoda. According to the WHO and FAO guideline different groups of insecticide applied for controlling pests in both the agricultural and public health sectors.

Methods: All the data published about resistant status of the mosquitoes Anopheles, Culex, Aedes and Culiseta species were searched on PubMed, Elsevier, Web of Science, Magiran and google scholar. The objectives of this study was to review the trend of resistance to insecticides during 2000–2020 in medically important mosquitoes in Iran. The criteria for resistant are followed according to WHO guideline.

Results: The Results showed that there are widespread, multiple resistances in the country to different organochlorine, organophosphates, carbamate and pyrethroids insecticides in the mosquitoes.

Conclusion: The effect of pesticide residues on the environment could be a cause for selection pressure on mosquitoes and lead to insecticides resistance to them. Insecticides resistance is main challenge of the vector control program. Also result will provide a guideline for control of the mosquito-borne diseases in the country as well as the world.

Keywords: Resistance; Insecticide; Mosquito; Iran

Introduction

Malaria is one of the most important parasitic diseases transmitted by the genus Anopheles to human (1-3). In Iran malaria has been present for a long time ago (4, 5) and mainly mentioned as a big public health challenge in Sistan and Baluchistan, Hormozgan and Kerman Provinces in the south-eastern part of Iran also featured as refractory malaria (6). The favorable results obtained in reducing of malaria transmissions by application of DDT for controlling of mosquito in a hyperendemic area in Iran for the first time in 1947 and then
spraying with DDT in combination with other vectors control interventions continued in the most malaria-endemic areas of the country until 1956, finally for first time in 1957 resistance to DDT was recorded in *Anopheles stephensi* as vector of malaria in Iran (4, 5). In Iran there are some species of malaria vectors (Fig. 1) including: *An. stephensi*, *An. dthali*, *An. culicifacies* s.l., *An. fluviatilis* s.l., *An. superpictus* s.l., *An. sacharovi*, *An. maculipennis* s.l. (3, 5). *Culex pipiens pipiens* and *Culex quinquefasciatus* as complex members of *Cx. pipiens* are competent vectors for some filarial and arboviral disease and also *Dirofilaria immitis* moreover West Nile and Sindbis viruses have been detected from mentioned species in Iran (1, 7-9). *Culex pipiens* habitat mainly is sewage system and there are different reagents and also residues of insecticides belong to several group of pesticides which have been previously used in agriculture and public health sectors (9, 10). For the first time resistance to insecticides was shown in 1975 in *Cx. pipiens pipiens* about DDT in the northern part of Iran (9, 11). *Fig. 2 shows the distribution of Cx. pipiens* and *Cx. quinquefasciatus* in Iran. After 20 years later from the first report of resistance to DDT in *An. stephensi*, this report was the second alarm related to resistance in medically important mosquitos in Iran. The presence of West Nile virus also has been reported in *Aedes caspius* or *Ochlerotatus caspius* from Iranian wetlands during recent years (12). Even though to date there is no report about the detection of pathogens among *Culiseta longiareolata* in Iran but, *Ae. caspius* (13) and *Cs. longiareolata* (14) currently showed their resistance to DDT. *Figs. 3 and 4 shows the distribution of Ae. caspius and Cs. longiareolata in Iran. Continuation of the previous report related to the appearance of insecticide resistance about DDT in *An. stephensi* and *Cx. pipiens* as vectors of important diseases in Iran. According to the latest studies only during 2012 to 2014 approximately 14,000 tons of pesticides consist of herbicides, insecticides, acaricides, and fungicides were used for agricultural pests (15). Due to the effect of pesticide residues on the environment it could be a cause for selection pressure on mosquitos which their breeding places are water and finally lead to their resistance to different group of insecticides indirectly (9, 10, 16). In the public health sector also different groups of insecticide applied for controlling *Anopheles* mosquitoes in malarious areas of Iran such as DDT and Dieldrin belong to organochlorine compounds, Malathion and Pirimiphos-methyl (organophosphates), Propoxur (carbamates), Deltamethrin and Lambda-cyhalothrin belong to pyrethroids compounds (4, 5). Previously for testing the insecticide susceptibility level among adult of mosquitos all bioassay studies have been performed referring to the test procedures of World Health Organization (WHO) recommended for insecticide resistance monitoring in mosquitos that suggested for each concentrations, six replicate samples of 20–25 adult female mosquitos per tube (2 replicates as control) shroud be expose for one hour at diagnostic dose of each insecticide and the number of mortality determined 24 hours after recovery period, finally the mortality results divided in three categories include: 98–100% mortality indicates susceptibility, 80–97% mortality considered as tolerance and also requires confirmation of resistance with other methods and if mortality was less than 80% in tested samples, mosquitos considered as resistant to insecticide (17). Previous guideline was revised recently and considering the current WHO categories for susceptibility level, the following criteria have been used for interpretation of results related to mortality rate: higher than 98% was considered as susceptible, mortality between 90% to 97% considered as resistance candidate and more investigation is needed for the confirmation of resistance and finally mortality less than 90% demonstrated resistance (18). Here there are examples regarding resistance to DDT lonely in medically important mosquitos and its trend from the beginning of the resistance to insec-
ticides. In the present paper, we aimed to review the trend of resistance to insecticides during 2000–2020 in medically important mosquitoes and also the distribution of resistant specimen plotted using Arc-GIS10.2 software (Redlands, CA) in Iran.

Materials and Methods

All the data published about resistant status of mosquitoes Anopheles, Culex, Aedes and Culiseta species were searched during 2000–2020 on PubMed, Elsevier, Web of Science, Magiran and google scholar.

Results

Review of resistance to insecticides in Anopheles mosquitoes as malaria vectors

According to recent studies, seven species of Anopheles mosquitoes (Fig. 1) introduced as malaria vectors in Iran including: An. stephensi, An. culicifacies s.l., An. flaviatilis s.l., An. superpictus s.l., An. dthali, An. sacharovi and An. maculipennis s.l. while An. pulcher-rinus is considered as a suspect vector moreover five of these vectors can be found in the southeast of the country, where the majority of malaria cases is reported also An. stephensi considered to be the main malaria vector in the same area (3, 19). The resistant status of Anopheles mosquitoes to organochlorine compounds in Iran (Table 1 and Figs. 5–7) indicated that approximately all malaria vectors in Iran were resistant to the DDT and Dieldrin which have been used previously for control of mosquitoes (6, 13, 20-37). After the first report about resistance to DDT in An. stephensi in 1957 other malaria vectors gradually, showed their resistance to organochlorine compounds in Iran up to now. But about An. sacharovi and An. maculipennis s.l. as main malaria vectors in the northern part of the country, all studies which have been performed on the susceptibility level of these species to organochlorine compounds showed tolerance to dieldrin (21, 23, 30, 33). Similar to this finding about Dieldrin, tolerance to DDT in An. dthali in south eastern part of Iran also has been shown (13). Although in some districts in southern parts of the country in Jiroft District in Kerman Province An. stephensi was tolerant to DDT and dieldrin (27). Moreover, in Bashagard District in Hormozgan Province tolerant to dieldrin in An. stephensi as well as tolerant to DDT in An. culicifacies s.l. also have been shown (28, 29).

The susceptibility level of Anopheles mosquitoes about pyrethroids insecticides such as deltamethrin, permethrin and etofenprox also have been reported in An. stephensi in this area (31, 34). Tolerant to deltamethrin also have been shown in An. stephensi, An. culicifacies s.l. and An. dthali in Bashagard District and An. stephensi in Jask District in Hormozgan Province (28, 35) and also in An. culicifacies s.l. in Chabahar District in Sistan and Baluchistan Province (36). Similar to mentioned finding about tolerant to pyrethroids insecticides in Anopheles mosquitoes, tolerant to deltamethrin and permethrin also has been shown in An. maculipennis in the northern part of Iran (33).

The susceptibility level of Anopheles mosquitoes to organophosphates compounds (Table 3 and Fig. 7) indicated that An. maculipennis s.l. in West Azarbaijan Province in the Northwestern part of the country has become resistant to Malathion (33) but about other Anopheles mosquitoes tolerant to Malathion in southern part also in An. dthali in Hormozgan Province (28) and also in An. stephensi and An. culicifacies s.l. in Sistan and Baluchistan Province were shown (13).

The status of Anopheles mosquito resistant to carbamates compound’s (Table 4 and Figs. 6, 7) indicated that among all malaria vectors
around the country resistance to carbamates insecticides such as propoxur and bendiocarb is shown in An. maculipennis s.l. in Northwestern part and resistance to bendiocarb in An. stephensi is in the southern part of the country (33, 37). Although in An. stephensi, An. culicifacies s.l. and An. dthali tolerant to propoxur in some parts of the country has been reported (13, 22, 28). By reviewing the resistance status of Anopheles mosquitoes during 2000 to 2020 it is concluded that approximately all Anopheles mosquitoes found resistance to organochlorine insecticides in Iran and although about other classes of insecticides there are a few reports for resistance about some malaria vectors to one or more insecticides, but considering the modification of the guideline for susceptibility test in mosquitos From 2013 which demonstrated resistance in mosquitos with mortality less than 90%, susceptible species in previous studies can be categories as resistant to insecticides (36).

**Review of resistance to insecticides in Culex mosquitoes**

The susceptibility level of Culex mosquitoes against organochlorine compounds in Iran (Table 5 and Figs. 8–10) revealed that Cx. pipiens, Cx. quinquefasciatus and Cx. theileri in most area of the country showed their high-level of insecticide resistance to DDT and deildrin (9, 13, 14, 16, 38, 39, 41, 42). Although, Cx. quinquefasciatus in a study in Southeast area showed its 90% mortality rate to DDT and according to the WHO considered as tolerant or candidate for resistance (40), similar Anopheles species, resistance to DDT in Culex mosquitoes around the country have been developed during recent years after the first report for resistance to DDT in the northern part of Iran about Cx. pipiens pipiens in 1975 (9, 11).

The status of Culex mosquitoes resistant to pyrethroids compound’s (Table 6 and Figs. 8–10) showed that they are almost resistant to most insecticides belong to pyrethroids (9, 13, 14, 39, 41-43). For example, in the north of Iran, Cx. pipiens in Sari District was highly resistance to all tested pyrethroids insecticides including Cyfluthrin, Lambda-cyhalothrin, Deltamethrin, Etofenprox and Permethrin (41).

Resistance to organophosphates compounds in Culex mosquitoes (Table 7 and Figs. 8, 9) indicated that members of Cx. pipiens complex were found resistant to Malathion and Fenitrothion (40, 41) although in Ahar District in East Azarbaijan tolerance to malathion in Cx. pipiens and Cx. theileri have been reported (14).

The susceptibility level of Culex mosquitoes to carbamates compounds (Table 8 and Figs. 8–10) revealed that Cx. quinquefasciatus, Cx. theileri and Cx. pipiens were found to be resistant to all tested insecticides belong to carbamates compounds (14, 16, 40, 41).

Comparing the resistance status of Culex mosquitoes with Anopheles mosquitoes during the past 20 years ago revealed that Culex species almost were found resistant to most insecticides belong to pyrethroids and also about other classes of insecticides the number of species which showed resistance to insecticides are more than Anopheles mosquitoes.

**Review of resistance to insecticides in Aedes caspius**

The resistance status of Ae. caspius to different groups of insecticides in Iran (Table 9 and Fig. 11) showed that Ae. caspius is resistant to DDT, Bendiocarb, Malathion, Permethrin and Lambdacychalothrin (13, 44). Actually this species was found to be resistant to all classes of insecticides although in some part this species was susceptible to deltame-thrin (44).

**Review of resistance to insecticides in Culiseta longiareolata**

The susceptibility level of Cs. longiareolata to different groups of insecticides (Table 10 and Fig. 12) indicated that this species similar Ae. caspius was resistant to all classes of insecticides (14, 45). There are a few studies about the susceptibility level of Cs. longiareolata and Ae. caspius in Iran, but both of them were found to be resistant to all groups of in-
secticides. In the following resistance to insecticides in medically important mosquitoes in Iran resistance to insecticides in mentioned species also can be considered as a problem in the vector control program.

Fig. 1. Distribution of malaria vectors in Iran
Table 1. List of Anopheles mosquitoes resistant to organochlorine compounds in Iran using the WHO insecticide susceptibility tests (2000–2020)

| Species            | Insecticides     | Location (Province-District) | References |
|--------------------|------------------|------------------------------|------------|
| An. pulcherrimus   | Dieldrin         | Sistan and Baluchistan-Ghasreghand | 20         |
| An. sacharovi      | DDT              | West Azerbaijan-Poldasht     | 21         |
| An. stephensi      | DDT              | Sistan and Baluchistan-Iranshahr | 22         |
| An. Sacharovi      | DDT              | East Azerbaijan-Kahnooj      | 23, 30     |
| An. stephensi      | DDT, Dieldrin    | Kerman-Kalibar              | 24         |
| An. stephensi      | DDT              | Hormozgan-Siahoo, Geno and Bandar Abbas | 25, 26 |
| An. stephensi      |                  | Fars-Kazeroon               |            |
| An. stephensi      |                  | Sistan and Baluchistan-Iranshahr | 27, 28, 29 |
| An. stephensi      |                  | Hormozgan-Bandar Abbas      |            |
| An. stephensi      |                  | Gilan-Astara                | 31         |
| An. superpictus s.l.|                  | West Azerbaijan               | 32         |
| An. superpictus s.l.|                  | Sistan and Baluchistan-Sarbaz | 33         |
| An. stephensi      |                  | Hormozgan-Jask              | 34, 37     |
| An. maculipennis s.l.|                  | Malathion                    | 35         |

Table 2. List of Anopheles mosquitoes resistant to pyrethroids compounds in Iran using WHO insecticide susceptibility tests (2000–2020)

| Species            | Insecticides     | Location (Province-District) | References |
|--------------------|------------------|------------------------------|------------|
| An. stephensi      | cyfluthrin, Imbda-cyhalothrin | Sistan and Baluchistan-Chabahar | 31, 34 |
| An. stephensi      | Imbdcyhalothrin  | Hormozgan-Jask               | 35         |

Table 3. List of Anopheles mosquitoes resistant to organophosphates compound’s in Iran using WHO insecticide susceptibility tests (2000–2020)

| Species                | Insecticides | Location (Province-District) | References |
|------------------------|--------------|------------------------------|------------|
| An. maculipennis s.l.  | Malathion    | West Azerbaijan              | 33         |

Fig. 2. Distribution of Culex pipiens and Culex quiquefasciatus in Iran
Table 4. List of *Anopheles* mosquitos resistant to Carbamates compound’s in Iran using WHO insecticide susceptibility tests (2000–2020)

| Species                | Insecticides          | Location (Province-District)            | References |
|------------------------|-----------------------|------------------------------------------|------------|
| *An. maculipennis* s.l.| Propoxur and Bendiocarb | West Azerbaijan                          | 33         |
| *An. stephensi*        | Bendiocarb            | Sistan and Baluchistan-Chabahar          | 37         |

Table 5. List of *Culex* mosquitos resistant to organochlorine compounds in Iran using WHO insecticide susceptibility tests (2000–2020)

| Species                  | Insecticides | Location (Province-District)          | References |
|--------------------------|--------------|---------------------------------------|------------|
| *Cx. theileri, Cx. pipiens* | DDT          | Tehran-Tehran                         | 38         |
| *Cx. quinquefasciatus*   | DDT          | Tehran-Varamin                         | 16         |
| *Cx. pipiens*            | DDT          | Sistan and Baluchistan-Chabahar        | 13         |
| *Cx. theileri* and *Cx. pipiens* | DDT     | East Azarbaijan -Ahar                 | 14         |
| *Cx. pipiens*            | DDT          | West Azerbaijan -Urmia                 | 39         |
| *Cx. pipiens*            | DDT          | Tehran-Tehran                          | 9          |
| *Cx. pipiens*            | DDT, Dieldrin | Mazandaran-Sari                        | 41         |
| *Cx. quinquefasciatus*   | DDT          | Hormozgan-Suru                         | 42         |

**Fig. 3.** Distribution of *Aedes caspius* in Iran
Table 6. List of *Culex* mosquitoes resistant to pyrethroids compound’s in Iran using WHO insecticide susceptibility tests (2000–2020)

| Species                  | Insecticides                        | Location (Province-District)                       | References |
|--------------------------|-------------------------------------|---------------------------------------------------|------------|
| *Cx. pipiens*            | Cyfluthrin and Lambdaacyhalothrin   | Sistan and Baluchistan-Chabahar                    | 13         |
| *Cx. theileri, Cx. pipiens* | Lambdaacyhalothrin               | East Azarbaijan-Ahar                               | 14         |
| *Cx. pipiens*            | Deltamethrin                        | West Azerbaijan-Urmia                               | 39         |
| *Cx. pipiens*            | Cyfluthrin, Lambdaacyhalothrin,     | Tehran-Tehran                                      | 9          |
|                          | Deltamethrin                        |                                                    |            |
| *Cx. pipiens*            | Cyfluthrin, Lambdaacyhalothrin,     | Mazandaran-Sari                                    | 41         |
|                          | Deltamethrin, Etofenprox, Permethrin|                                                    |            |
| *Cx. quinquefasciatus*   | Deltamethrin                        | Hormozgan-Suru                                     | 42         |
| *Cx. pipiens complex*    | Deltamethrin                        | Tehran-Gharchak                                    | 43         |

Table 7. List of *Culex* mosquitoes resistant to organophosphates compound’s in Iran using WHO insecticide susceptibility tests (2000–2020)

| Species                  | Insecticides           | Location (Province-District)   | References |
|--------------------------|------------------------|--------------------------------|------------|
| *Cx. quinquefasciatus*   | Malathion              | Kerman-Rafsanjan                | 40         |
| *Cx. pipiens*            | Malathion, Fenitrothion| Mazandaran-Sari                 | 41         |

Fig. 4. Distribution of *Culiseta longiareolata* in Iran

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Table 8. List of Culex mosquitos resistant to carbamates compounds in Iran using WHO insecticide tests (2000–2020)

| Species                      | Insecticides | Location (Province-District) | References |
|------------------------------|--------------|------------------------------|------------|
| Cx. theileri and Cx. pipiens | Propoxur     | East Azarbaijan-Ahar         | 14         |
| Cx. quinquefasciatus         | Bendiocarb   | Tehran-Varamin               | 16         |
| Cx. quinquefasciatus         | Bendiocarb   | Kerman-Rafsanjan             | 40         |
| Cx. pipiens                  | Bendiocarb   | Mazandaran-Sari              | 41         |

Table 9. Resistance status of Aedes caspius to different groups of insecticides in Iran using WHO insecticide susceptibility tests (2000–2020)

| Species     | Insecticides | Location (Province-District) | References |
|-------------|--------------|------------------------------|------------|
| Ae. caspius | DDT          | Sistan and Baluchistan-Chabahar | 13         |
|             |              | Hormozgan-Siahoo             | 44         |
|             | Malathion    | Sistan and Baluchistan-Chabahar | 44         |
|             | Bendiocarb   | Hormozgan-Siahoo             | 44         |
|             | Permethrin, lambdacyhalothrin | Hormozgan-Siahoo             | 44         |

Fig. 5. Distribution of Anopheles mosquitos with resistance to organochlorine compounds in Iran (2000–2020)
Fig. 6. Distribution of Anopheles stephensi with resistance to different insecticides in Iran (2000–2020)

Fig. 7. Distribution of Anopheles maculipennis with resistance to different insecticides in Iran (2000–2020)
Table 10. Resistance status of *Culiseta longiareolata* to different groups of insecticides in Iran using WHO insecticide susceptibility tests (2000–2020)

| Species        | Insecticides          | Location (Province-District) | References |
|----------------|-----------------------|-----------------------------|------------|
| *Cs. longiaerolata* | DDT                  | East Azarbaijan-Ahar        | 14         |
|                | Propoxur              | East Azarbaijan-Marand      | 45         |
|                | Deltamethrin          | East Azarbaijan-Ahar        | 14         |
|                | Fenitrothion          | East Azarbaijan-Marand      | 45         |

Fig. 8. Distribution of *Culex quinquefasciatus* with resistance to different insecticides in Iran (2000–2020)
Fig. 9. Distribution of *Culex pipiens* with resistance to different insecticides in Iran (2000–2020)
Fig. 10. Distribution of *Culex theileri* with resistance to different insecticides in Iran (2000–2020)

Fig. 11. Distribution of *Aedes caspius* with resistance to different insecticides in Iran (2000–2020)
Discussion

The trend of insecticides resistance in medically important mosquitoes in Iran revealed that among specimens of Anopheles mosquitoes as malaria vectors, approximately all of them have been found resistant to one or more insecticides and also most malaria vectors are resistant to the organochlorine compounds in Iran. It cannot conclude certainly that all the malaria vectors are resistant to insecticide because there are no definite report about resistance to insecticides in An. fluvialis s.l. and An. dthali although there are some reports about tolerant in An. dthali to some insecticides. In Iran, An. stephensi as the main malaria vector has been found resistant to most classes of insecticides during recent years and this resistance may be caused by others intervention for controlling of malaria vectors such as Indoor Residual Spraying (IRS) and Insecticide Treated Nets (ITNs) or usage of insecticide in the agriculture sector (34). Resistance to all classes of insecticides also reported in other countries in An. stephensi for example in Afghanistan, An. stephensi has been found resistant to DDT, malathion, bendiocarb, deltamethrin, and permethrin and in Ethiopia, it was highly resistant to deltamethrin, permethrin pirimiphos-methyl, malathion, DDT, propoxur, and bendiocarb (46, 47). Similar finding of Anopheles mosquitos, Culex specimens also were resistant to several insecticides belong to each class moreover Cx. pipiens in the north of Iran, in Mazandaran Province was high.
resistance to all tested insecticides of all major classes (41) around the world some studies also reported a high level of resistance in members of *Cx. pipiens* complex to many groups of insecticides (48-50). Based on the literature, there were no reports available on monitoring the susceptibility level of *Ae. caspius* and *Cs. longiaerolata* to insecticides which recommended by WHO around the world. Recent studies about baseline susceptibility of mentioned species in Iran revealed that both of these mentioned species were found to be resistant to all classes of insecticides in the study areas of *Ae. caspius* and *Cs. longiaerolata* (13, 14, 44, 45). During recent years the development of resistance to insecticides in mosquitos as vectors of important diseases in Iran were increased. So that almost all medically important mosquitos were found to be resistant to all different classes of insecticides. The use of alternative insecticide which is made from natural products and some biological agents can be appropriates method for vectors control programs (45, 51, 52). Secondary metabolites of plants such as essential oils are candidates for the discovery of new compounds against vector mosquitoes. Insecticide-based plants have the advantage of exhibiting novel modes of action against mosquito vectors that could lessen the risk of resistance (45, 52-61). Moreover, for controlling of mosquito populations, *Wolbachia* as an intracellular organism that infect different groups of arthropods, also introduced as a bioagent due to its environmentally friendly feature (62, 63).

**Conclusion**

Relevant studies about resistance to insecticides during the quarter of a century about medically important mosquitos in Iran indicated that the development of resistance to all classes of insecticides in mosquitos is happening gradually, so alternative and efficient intervention methods should be used to preventing the development of resistance to insecticides in mosquitos.

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