



SYSTEMATIC REVIEW

REVISED Current status of insecticide resistance in malaria vectors in the Asian countries: a systematic review [version 2; peer review: 1 approved, 2 approved with reservations]

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Abstract

Background: The application of insecticides for malaria vector control has led to a global problem, which is the current trend of increased resistance against these chemicals. This study aimed to review the insecticide resistance status was previously determined in Asia and how to implement the necessary interventions. Moreover, the implications of resistance in malaria vector control in this region were studied.

Methods: This systematic review was conducted using a predefined protocol based on PRISMA-retrieved articles from four science databases, namely ProQuest, Science Direct, EBSCO, and PubMed in the last ten years (2009 to 2019). The searching process utilized four main combinations of the following keywords: malaria, vector control, insecticide, and Asia. In ProQuest, malaria control, as well as an insecticide, were used as keywords. The following criteria were included in the filter, namely full text, the source of each article, scholarly journal, Asia, and publication date as in the last ten years.

Results: There were 1408 articles retrieved during the initial search (ProQuest=722, Science Direct=267, EBSCO=50, PubMed=285, and Scopus=84). During the screening, 27 articles were excluded because of duplication, 1361 based on title and abstract incompatibility with the inclusion criteria, and 20 due to content differences. In the final screening process, 15 articles were chosen to be analyzed. From the 15 articles, it is known that there was organochlorine (DDT), organophosphate (malathion), and pyrethroids resistance in several Anopheles species with a less than 80% mortality rate.

Conclusion: This review found multiple resistance in several Anopheles includes resistance to pyrethroid. The reports of pyrethroid resistance were quite challenging because it is considered effective in the malaria vector control. Several countries in Asia are implementing an insecticide resistance management (IRM) strategy against malaria vectors following the Global Plan for IRM.

Open Peer Review

Reviewer Status

	Invited Reviewers		
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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Anopheles; Malaria Elimination; Vector Control Program; Insecticide Resistance; Asian Countries

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REVISED Amendments from Version 1

This manuscript is a revision version. The revision was based on reviewers' comments and suggestions. It is shown from abstract to conclusion, and also, there are several additional references to conform all the words. The important thing is the conclusion; this is drawn from the article selected. There are new titles given; the results and discussion improved; all revisions are based on the reviewers' comments and suggestions. We hope this paper will be more readable and understandable for others.

Any further responses from the reviewers can be found at the end of the article

Introduction

Malaria is one of the most common vector-borne diseases widespread in the tropics and subtropics¹. According to the World Malaria Report (2020), an estimated that around 229 million cases of malaria in 2019 in 87 Malaria endemic countries, declined from 238 million in 2000 in 108 countries which were malaria endemic in 2000. Malaria death has been reduced in the period 2000–2019, from 736,000 in the year 2000 to 409,000 in 2019². The global estimate of deaths caused by malaria reached 435,000 cases, which was the same number in 2016³. The use of insecticides is the basis for the effective control of vectors, and this process has played an essential role in the management and elimination of malaria⁴.

The prevention of malaria depends on four classes of insecticides mainly one class of insecticides, namely pyrethroids; however, the increase in resistance to it reduces this treatment's efficacy and it is dangerous⁵. The progressive reduction of malaria's burden through substantial improvements of insecticide-based vector control in recent years is partly reversible by the emergence of widespread resistance to this chemical⁶. Insecticide resistance is widespread and is now reported in almost two-thirds of the countries with ongoing malaria transmission. This resistance affects all major vector species and groups of insecticides⁷.

Vector control is an essential aspect of a program organized to manage the disease transmitted by *Anopheles* mosquitoes. The use of insecticides for this process is an effective strategy; however, it is also related to the development of resistance in targeted vectors and is one reason for the failure of disease control in many countries⁸. Since 2000, malaria cases have halved due to the management and vector control interventions, estimated to have saved 660 million people⁹. The global commitment to eliminate malaria by 2030 requires immediate efforts that include the establishment of infrastructure for regular monitoring insecticide resistance, the development of combined and effective control products¹⁰.

This review aimed to determine the status of insecticide resistance in Asia and how to implement interventions. It is also expected that this sets an example for other countries in the vector control program and provides guidance for insecticides and malaria risk reduction.

Methods

Search strategy

This study retrieved articles from four science databases, namely ProQuest, Science Direct, EBSCO, and PubMed, from December 2009 to December 2019. A systematic review was conducted using a predefined protocol based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA)^{11,12}. The searching process utilized four main combinations of the following keywords: “malaria”, “vector control”, “insecticide”, and “Asia”. In order to reduce the risk of bias from the articles obtained, the researchers conducted disbursements in all databases using the same keywords and on the same day.

In ProQuest, “malaria” and “vector control”, as well as “insecticide”, were used as keywords. The full text, the source of an article, scholarly journal, Asia, and date of publication as in the last ten years were included in the filter. The search strategy and filter used in Science Direct were the same as that above except “Asia”. In EBSCO, a similar keyword was also used. The limiters were the same as the filter in the ProQuest, but also included “abstract available”. In the PubMed, the terms used were as follows, (“malaria”[MeSH Terms] OR “malaria”[All Fields]) AND (“vector”[MeSH Terms] OR “vector”[All Fields]) AND (“control”[MeSH Terms] OR “control”[All Fields]) AND (“insecticide”[MeSH Terms] OR “insecticide”[All Fields]) AND (“loattrfulltext”[sb] AND “2009/12/02”[Pdat] : “2019/12/02”[Pdat])s.

Inclusion and exclusion criteria

Original articles (academic or research papers) in Asia, written in English and published in the last ten years were included. Study designs such as prospective study, review, cross-sectional, cohort, and case-control were included. Articles about biochemical, resistance to dieldrin (RDL) mutation, knowledge and attitudes, and spatial modeling were excluded because that can cause different results. Articles about malaria but including nothing about insecticides were excluded. The implications of insecticide resistance in related countries were investigated. Studies that were not relevant to this study were excluded.

Study selection

The articles' eligibility was determined from each title, abstract, and full text by two reviewers (DP and DS). DP and DS also independently screened the articles for inclusion and extracted data on general information. To solve any disagreements and problems during the study, regular meetings were held by the researchers to discuss issues.

Data extraction and analysis

The search strategy and inclusion and exclusion criteria were validated and implemented. The initial database was then created from the electronic search. All citations were first filtered by title and abstract, and duplicates omitted. The full texts of eligible papers were then obtained independently for further filtering. After resolving the differences in data extraction or interpretation through consensual discussions based on the inclusion and exclusion criteria mentioned above, the final papers were selected.

The data from the chosen eligible studies were the authors, study period, year of publication, the country where it was conducted, study period, publisher, settings, location characteristics, bioassay methods, the sample of *Anopheles* mosquito, and habitat. The findings were arranged according to the objective and results obtained in related implications of malaria vector control resistance. Throughout the entire selection process, the use of insecticides in the bioassay method, the associated mortality rate of the *Anopheles* mosquito, and its implementation in the specific areas were reported to illustrate the practice's pattern and extent.

All variables for which we extracted data were *Anopheles* species, vector habitat, bioassay method, insecticides, mortality rate, insecticide resistance strategies/intervention. The differences in methods could bias the results; to reduce this bias, we selected articles with a similar method. For articles about insecticide resistance, we only looked at articles using bioassay with the world health organization (WHO) standard¹³. Even though currently the CDC bottle assay is also used for insecticide resistance testing and monitoring, there was no selected articles used CDC bottle assay for testing insecticide resistance and monitoring. The WHO bioassay is carried out with paper impregnated from four main classes of insecticides in common use, with different concentrations according to the WHO test procedure¹⁴.

Results

A map showing the countries where insecticide resistance has been reported and the recorded resistance status for each insecticide used is missing shown in Figure 1¹⁵. There were 1,408 articles retrieved during the initial searching (ProQuest=722, Science Direct=267, EBSCO=50, PubMed=285 and Scopus=84). Through screening, 27 articles were excluded because of duplication, 1,361 based on title and abstract incompatibility and 20 due to inconsistency with the inclusion criteria; 15 were chosen to be analyzed.

The 15 eligible articles originated from eight Asian countries published from 2012 to 2019 journals are shown in Table 1.

There were 23 species of *Anopheles* from these studies (Table 2). The main vectors included *An. stephensi* (Iran), *An. superpictus* (Afghanistan), *An. culicifacies* (India), *An. minimus* and *An. maculatus* (Lao and Thailand), *An. sinensis* (China), *An. subpictus* (Sri Lanka), and *An. sacharovi* (Turkey). From Table 2, the habitat of malaria vector was divided into four habitats: 1) Agriculture: rice fields (paddy fields), 2) Mountains (forest), 3) Aquatic habitat (rivers, ponds, streams, swamps), and 4) Coastal (seaport). In India, *An. culicifatus* was found only in the forest, but *An. annularis* was found in the forest an irrigation pond. *Anopheles culicifatus* in Afghanistan was found together with *An. stephensi* and *An. superpictus* at agriculture and aquatics habitat. *Anopheles annularis* was also found in Thailand on Agriculture (paddy fields). In Iran, there was only *An. stephensi* was found in coastal areas and ports. In coastal and inland Sri Lanka was discovered *An. subpictus* and *An. sundaicus*. In Thailand and Lao, many species were found in forests and agriculture (paddy fields) such as *An. annularis*, *An. minimal*,

An. hyrcanus, *An. barbirostris*, *An. vagus*, *An. maculatatus*, *An. jamessi*, *An. scanloni*, *An. kochi*, *An. tessellatus*, *An. dirus*, *An. karwari*, *An. nivipes*, *An. vagus*, *An. philipinensis*. As same as in Thailand, in Lao there were also many species of *Anopheles* in the same habitat, except *An. umbrosus* and *An. aconitus* were in Lao and *An. jamessi*, *An. scanloni* in Thailand. In China, there were two species in mountains, aquatics habitat, and agriculture; they were *An. sinensis* and *An. vagus*. *Anopheles superpictus*, besides being found in Afghanistan, also in Turkey together with *An. sacharovi* on the farm, waters, and swamps. The differences in the main vector of each country depended on environmental/ecological conditions, living habitat, as well as the feeding and resting behavior of each *Anopheles*.

All the female *Anopheles* collected were morphologically identified for their species/complexes using stereomicroscopes and morphological keys¹⁶. The mosquitoes were separated by species/complexes for bioassays. The mosquitoes kept alive by giving them a sugar solution¹⁷.

Anopheles mosquitoes were morphologically identified at the adult stage using the Glick identification key¹⁸. The susceptibility tests were carried out following the WHO guidelines for monitoring resistance in malaria vectors. From 15 papers reviewed, the papers impregnated with insecticides of DDT (4%), malathion (5%), bendiocarb (0.1%), propoxur (0.1%), deltamethrin (0.05%) and I-cyhalothrin (0.05%), cyfluthrin 0.15%, permethrin 0.75%, and etofenprox 0.5% were prepared by adopting the WHO standard method¹⁴ (Table 3).

The insecticide bioassay was then carried out using a recommended standard WHO kit¹³. The mortality rate was recorded 24 hours after exposure, while the average death was calculated for each insecticide and according to the WHO criteria¹⁹. Bioassay results according to the WHO criteria are susceptible ($\geq 98\%$ mortality), possible resistance (90–97% mortality) or confirmed resistance ($<90\%$ mortality)¹³.

The highest mortality rate (MR) $\geq 98\%$ of etofenprox application was on *An. stephensi* in Iran. While permethrin application was on *An. superpictus* (Afghanistan), *An. nivipes* (Thailand), *An. philipinensis* (Lao and Thailand), and *An. tessellatus* (Lao). Then, bendiocarb and malathion were on *An. culicifacies* (India and Afghanistan). Also, deltamethrin was on *An. annularis* (India), *An. barbirostris*, *An. dirus*, *An. karwari* (Thailand), *An. vagus* (Thailand and China), *An. maculatus* (Lao and Thailand), and *An. umbrosus* (Lao). *An. minimus* (Thailand Myanmar Border), Meanwhile, permethrin and deltamethrin were on *An. aconitus*, and *An. kochi* (Lao). Lastly, lambda cyalothrin and deltamethrin were on *An. sundaicus* (Sri Lanka), with MR $\leq 97\%$ indicating resistance-possibility based on the WHO classification.

Table 4 shows the level of *anopheles* resistance to organochlorine (dichlorodiphenyltrichloroethane; DDT), organophosphate (malathion), carbamate (bendiocarb and propoxur), and pyrethroid (permethrin, deltamethrin, lambda cyalothrin, cyfluthrin, and etofenprox). Almost all the species of this mosquito studied were possibly resistant to DDT. Furthermore, this similar

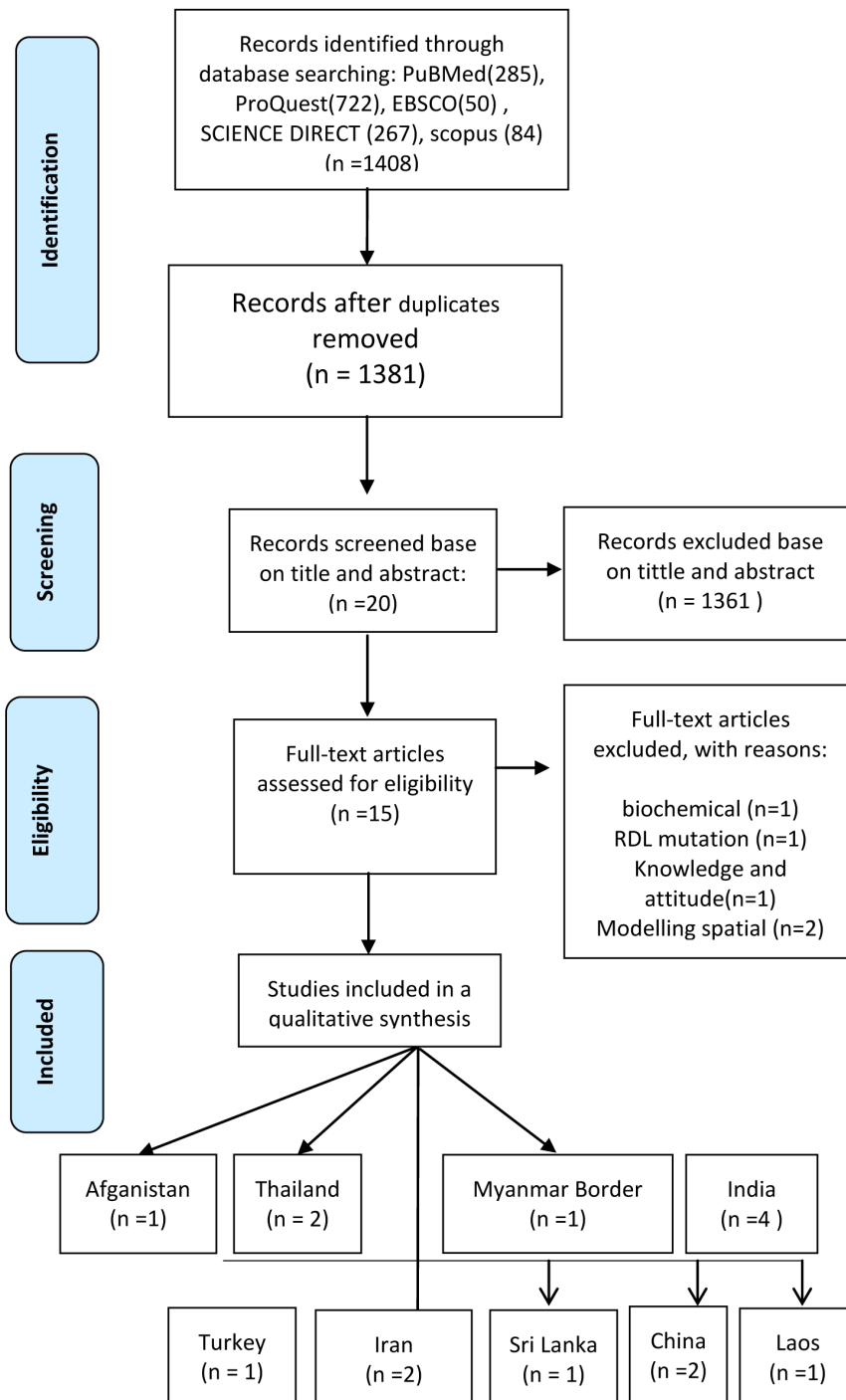


Figure 1. PRISMA flow diagram of systematic review inclusion and exclusion process.

issue has been reported in *An. stepensi*, *An. superpictus*, *An. culicifacies*, *An. vagus*, *An. sinensi*, *An. subpictus*, and *An. sachrovi* to malathion. Also, it was found in *An. superpictus* and *An. sachrovi* to propoxur as well as in *An. umbrosus* to permethrin. The same was in *An. sinensis*, *An. superpictus*, *An. sundaicus*,

An. minimus, *An. maculatus* and *An. jamessi* to deltamethrin. Resistance was also reported in *An. stephensi*, *An. culicifacies*, *An. vagus*, and *An. barbirostris* to permethrin and deltamethrin, and in *An. stephensi* to etofenprox. However, direct resistance was found in *An. hyrcanus* to Permethrin and deltamethrin, as

Table 1. Article description.

Authors	Title	Year of publication	Country	Study periods	Publisher	Reference
Ahmad <i>et al.</i>	Status of insecticide resistance in high-risk malaria provinces in Afghanistan.	2016	Afghanistan	August to October 2014	Malaria Journal	20
Mishra <i>et al.</i>	Insecticide resistance status of <i>Anopheles culicifacies</i> in Madhya Pradesh, central India	2012	India	August to September 2009	Journal of Vector-Borne Diseases	8
Dhiman <i>et al.</i>	Insecticide resistance and human blood meal preference for <i>Anopheles annularis</i> in Asom-Meghalaya border area, northeast India	2014	India	June–August 2011	Journal of Vector-Borne Diseases	21
Sahu <i>et al.</i>	Triple insecticide resistance of <i>Anopheles culicifacies</i> : A practical impediment for malaria control in Odisha State, India.	2015	India	April to June 2014	Indian Journal of Medical Research	19
Chand <i>et al.</i>	Insecticide resistance status of <i>An. culicifacies</i> in Gadchiroli (Maharashtra) India	2017	India	August 2016 and February 2017	Pathogens and global health	22
Chareonviriyaphap <i>et al.</i>	Review of insecticide resistance and behavioral avoidance of human diseases by vectors in Thailand	2013	Thailand	2000–2010	Parasites & Vectors	23
Chaumeau <i>et al.</i>	Insecticide resistance of malaria vectors along the Thailand-Myanmar border	2017	Thailand	August and November 2014, July 2015	Parasites & Vectors	24
Sumarnrote <i>et al.</i>	Insecticide resistance status of <i>Anopheles</i> mosquitoes in Ubon Ratchathani province, Northeastern Thailand	2017	Thailand	September 2013–September 2015	Malaria Journal	17
Gorouhi <i>et al.</i>	Biochemical Basis of Cyfluthrin and DDT Resistance in <i>Anopheles stephensi</i> (Diptera: Culicidae) in Malarious Area of Iran	2018	Iran	April–June 2015	Journal of Arthropod-Borne Diseases	25
Vatandoost <i>et al.</i>	Indication of pyrethroid resistance in the main malaria vector, <i>Anopheles stephensi</i> from Iran	2012	Iran	Spring 2011	Asian Pacific Journal of Tropical Medicine	26
Marcombe <i>et al.</i>	Insecticide resistance status of malaria vectors in Lao PDR	2017	Lao	The rainy (June to October) and dry (January to May) seasons of 2014 and 2015	PloS One	27
Qin <i>et al.</i>	Insecticide resistance of <i>Anopheles sinensis</i> and <i>An. vagus</i> in Hainan Island, a malaria-endemic area in China	2014	China	July–August 2012	Parasites & Vectors	28
Dai <i>et al.</i>	Development of insecticide resistance of malaria vector <i>Anopheles sinensis</i> in Shandong Province In China	2015	China	2003–2012	Malaria Journal	29
Surendran <i>et al.</i>	Variations in susceptibility to common insecticides and resistance mechanisms among morphologically identified species of the malaria vector <i>Anopheles subpictus</i> in Sri Lanka	2012	Sri Lanka	July 2008–June 2010	Parasites & Vectors	30
S.İ. Yavaşoğlu, <i>et al.</i>	Current insecticide resistance status of <i>Anopheles sacharovi</i> and <i>A. superpictus</i> in former malaria-endemic areas of Turkey	2019	Turkey	April 2014 and September 2015	Acta Tropica	31

Table 2. Mosquito species and their types of habitat.

Study location	Country	<i>Anopheles</i> species	Sample adult female mosquitoes (n)	Vector habitat	Reference
Nangarhar, Laghman, Kunar, Ghazni, and Badakhshan	Afghanistan	<i>An. stephensi</i> , <i>An. superpictus</i> , <i>An. culicifacies</i>	2049	Ricefield, river stream, ponds, and water puddle	20
Madhya Pradesh	India	<i>An. culicifacies</i>	NA	Forest	8
Asom-Meghalaya border area, northeast India	India	<i>An. annularis</i>	200	Forest, ponds irrigation	21
Rayagada, Nowrangpur, Kalahandi, Malkangiri and Koraput	India	<i>An. culicifacies</i>	1740	Forest	19
Gadchiroli district	India	<i>An. culicifacies</i>	NA	Forest	22
Chiang Mai-Chiang Dao, Mae Hongson, Phrae	Thailand	<i>An. minimus</i> <i>An. annularis</i>	NA	Paddy fields and rivulet	23
Thailand-Myanmar Border	Thailand	<i>An. annularis</i> , <i>An. minimus</i> , <i>An. hyrcanus</i> , <i>An. barbirostris</i> , <i>An. vagus</i> , <i>An. maculatus</i> , <i>An. jamessi</i> , <i>An. scanloni</i> , <i>An. kochi</i> , <i>An. tessellatus</i>	5896	Agriculture	24
Khong Chiam, Sirindhorn, Buntharik, and Nachaluay	Thailand	<i>An. hyrcanus</i> , <i>An. barbirostris</i> , <i>An. maculatus</i> , <i>An. nivipes</i> , <i>An. philipinensis</i> , <i>An. vagus</i> <i>An. dirus</i> <i>An. karwari</i>	2088	Forest and ricefield	17
Chabahar Seaport, southeast corner of Iran	Iran	<i>An. stephensi</i>	317	Seaport	25
Sistan and Baluchistan	Iran	<i>An. stephensi</i>	733	Coastal	26
Phongsaly, Bokeo, LuangPrabang, Vientiane Pro, Borlikhamxay, Khammouane, Savannakhet, Saravane, Sekong, Attapeu.	Lao	<i>An. minimus</i> , <i>An. hyrcanus</i> , <i>An. vagus</i> <i>An. maculatus</i> <i>An. nivipes</i> <i>An. philipinensis</i> <i>An. umbrosus</i> <i>An. kochi</i> <i>An. tessellatus</i> <i>An. aconitus</i>	3977	Forest, village, agriculture	27
Hainan Island	China	<i>An. sinensis</i> , <i>An. vagus</i>	1468	Mountainous and ricefield	28
Shandong Province	China	<i>An. sinensis</i>	4370	Irrigated ricefield, aquatic habitat, and small ponds	29
Batticaloa, Puttalam, Trincomalee and Ampara	Sri Lanka	<i>An. subpictus</i> <i>An. sudaicus</i>	256	Coastal and inland	30
Southeastern Anatolia and the Mediterranean	Turkey	<i>An. superpictus</i> , <i>An. sacharovi</i>	1230	Agricultural, ponds, stream and swamps	31

Table 3. The WHO bioassay method.

Country	WHO bioassay with insecticides										
	Organochlorine	Organophosphate			Carbamate		Pyrethroid				Etofenprox (%)
	DDT (%)	malathion (%)	Bendiocarb (%)	Propoxur (%)	Permethrin (%)	Deltamethrin (%)	Lambda-cyhalothrin (%)	Cyfluthrin (%)			
Afghanistan	4.0	5.0	0.1	NA	0.75	0.05	NA	NA	NA	NA	
India	4.0	5.0	NA	NA	NA	0.05	NA	NA	NA	NA	
India	4.0	NA	NA	NA	NA	0.05	NA	NA	NA	NA	
India	4.0	5.0	NA	NA	NA	0.05	NA	NA	NA	NA	
India	4.0	NA	NA	NA	0.75	0.05	0.05	0.15	NA	NA	
Thailand	4.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Thailand	4.0	NA	NA	NA	0.75	0.05	NA	NA	NA	NA	
Thailand	4.0	NA	NA	NA	0.75	0.05	NA	NA	NA	NA	
Iran	4.0	NA	NA	NA	0.75	0.05	0.05	0.15	0.5	0.5	
Iran	4.0	NA	NA	NA	0.75	0.05	0.05	0.15	0.5	0.5	
Lao	4.0	NA	NA	NA	0.75	0.05	NA	NA	NA	NA	
China	4.0	5.0	NA	NA	NA	0.05	NA	NA	NA	NA	
China	4.0	5.0	NA	NA	NA	0.05	NA	0.15	NA	NA	
Sri Lanka	4.0	5.0	NA	NA	NA	0.05	0.05	NA	NA	NA	
Turkey	4.0	5.0	NA	0.1	0.75	0.05	NA	NA	NA	0.5	

WHO=world health organization. DDT=dichlorodiphenyltrichloroethane. NA= not available.

Table 4. Anopheles mortality rates in insecticide resistance bioassays.

No	Anopheles species	Percentage of mortality (Susceptibility Status)											Reference		
		Organochlorine			Organophosphate		Carbamate		Pyrethroid					Etofenprox (%)	
		DDT (%)	Malathion (%)	Bendiocarb (%)	Propoxur (%)	Permethrin (%)	Deltamethrin (%)	Lambda-cyhalothrin (%)	Cyfluthrin (%)						
1	<i>An. stephensi</i> *	31-60 (R)	47-97 (R)	87-100 (PR)	NA	87-91 (PR)	66-78 (R)							20	
2	<i>An. superpictus</i> *	50-86.7 (R-PR)	61.7-88.3 (R-PR)		68.3-91.7 (R-PR)	NA	NA	NA	NA	NA	NA	NA	NA	NA	31
3	<i>An. culicifacies</i> *	100 (S)	100 (S)	92 (PR)	NA	100 (S)	85 (PR)	NA	NA	NA	NA	NA	NA	NA	20
		6.6-26.6 (R)	65.4-100 (R-S)	NA	NA	NA	71.6-94.1 (R-PR)	NA	NA	NA	NA	NA	NA	NA	8
		11.4-15.3 (R)	60.4-76.2 (R)	NA	NA	NA	72.6-84 (R-PR)	NA	NA	NA	NA	NA	NA	NA	19
		37.1 (R)	74 (R)	NA	NA	91.3 (PR)	83.8 (PR)	59.9 (R)	70.2 (R)	NA	NA	NA	NA	22	
		81 (PR)	95 (PR)	100 (S)		89 (PR)	64 (R)							20	
4	<i>An. annularis</i>	11.9-28.3 (R)	NA	NA	NA	NA	97.7-98.1 (PR-S)	NA	NA	NA	NA	NA	NA	21	
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	23	
		NA	NA	NA	NA	NA	100 (S)							24	
		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	23	
5	<i>An. minimus</i> *	NA	NA	NA	NA	NA	92 (PR)	NA	NA	NA	NA	NA	NA	24	
		98-100 (S)	NA	NA	NA	100 (S)	100 (S)	NA	NA	NA	NA	NA	NA	27	
		57 (R)	NA	NA	NA	48 (R)	33 (R)	NA	NA	NA	NA	NA	NA	24	
6	<i>An. hyrcanus</i> *	72-83 (R-PR)	NA	NA	NA	65-87 (R-PR)	45-85 (R-PR)	NA	NA	NA	NA	NA	NA	17	
		90 (PR)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	27	
		69 (R)	NA	NA	NA	NA	97-100 (PR-S)	NA	NA	NA	NA	NA	NA	17	
		74 (R)	NA	NA	NA	84 (PR)	72 (R)	NA	NA	NA	NA	NA	NA	24	
		34-61 (R)	NA	NA	NA	89-95 (PR)	79-95 (R-PR)	NA	NA	NA	NA	NA	NA	27	
		67.1-88.8 (R-PR)	77.3-88.9 (R-PR)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	28	
8	<i>An. vagus</i> *	97 (PR)	NA	NA	NA	95 (PR)	75 (R)	NA	NA	NA	NA	NA	NA	24	
		NA	NA	NA	NA	NA	97.9-100 (S)	NA	NA	NA	NA	NA	NA	28	
		NA	NA	NA	NA	NA	100 (S)	NA	NA	NA	NA	NA	NA	17	

No	Anopheles species	Percentage of mortality (Susceptibility Status)												Reference
		Organochlorine		Organophosphate		Carbamate		Pyrethroid				Etofenprox (%)		
		DDT (%)	Malathion (%)	Bendiocarb (%)	Propoxur (%)	Permethrin (%)	Deltamethrin (%)	Lambda-cyhalothrin (%)	Cyfluthrin (%)					
9	<i>An. maculatus*</i>	86-100 (PR-S)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	27
10	<i>An. jameasi</i>	NA	NA	NA	NA	NA	NA	97 (PR)	85 (PR)	NA	NA	NA	NA	24
11	<i>An. nivipes</i>	NA	NA	NA	NA	NA	NA	NA	100 (PR)	100 (PR)	NA	NA	NA	27
12	<i>An. philippinenses</i>	0-100 (R-S)	NA	NA	NA	NA	NA	90-100 (PR)	100 (S)	100 (S)	NA	NA	NA	17
13	<i>An. umbrosus</i>	63 (R)	NA	NA	NA	NA	NA	100 (S)	NA	100 (S)	NA	NA	NA	27
14	<i>An. sinensis*</i>	30.4 (R)	86.6 (PR)	NA	NA	NA	NA	NA	35.8 (R)	NA	NA	32.4 (R)	NA	29
15	<i>An. subpictus*</i>	72.7-78.4 (R)	NA	NA	NA	NA	NA	NA	85.8-91 (PR)	NA	NA	NA	NA	28
16	<i>An. sacharovi*</i>	16-35 (R)	58.3-90 (R-PR)	NA	NA	NA	NA	NA	82-96 (PR)	72-97 (R-PR)	NA	NA	NA	30
17	<i>An. scanloni</i>	84 (PR)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	31
18	<i>An. kochi</i>	82-100 (PR-S)	NA	NA	NA	NA	NA	100 (S)	100 (S)	NA	NA	NA	NA	24
19	<i>An. tessellatus</i>	NA	NA	NA	NA	NA	NA	NA	98 (S)	NA	NA	NA	NA	27
20	<i>An. sundaiacus</i>	14 (R)	NA	NA	NA	NA	NA	100 (S)	NA	NA	NA	NA	NA	24
21	<i>An. aconitus</i>	NA	93-98 (PR-S)	NA	NA	NA	NA	NA	98 (S)	NA	NA	NA	NA	30
22	<i>An. dirus</i>	38-47 (R)	NA	NA	NA	NA	NA	100 (S)	100 (S)	100 (S)	NA	NA	NA	27
23	<i>An. karwari</i>	100 (S)	NA	NA	NA	NA	NA	100 (S)	100 (S)	100 (S)	NA	NA	NA	17
		NA	NA	NA	NA	NA	NA	100 (S)	100 (S)	100 (S)	NA	NA	NA	17

*Main vector

DDT=dichlorodiphenyltrichloroethane. NA=not available, S=Susceptible (90-97% mortality suggest), P=Possible Resistance, R=Resistance= < 90%.

well as in *An. culicifacies* to lambda cyalothrin. Also, this was found in *An. stephensi*, *An. sinensis* and *An. culicifacies* to cyfluthrin.

Table 5 shows that the insecticide resistance management strategies in several Asian countries are through vector control by environmental, biological, and chemical interventions. The implementation of chemical interventions is through insecticide rotation, monitoring their bioefficacy, mapping, and surveillance of malaria vectors. Malaria eradication relies on effective prevention, technical capability approaches, government and community support, funding sources, accurate data, and adequate implementation.

Discussion

Study sites

Ecologically, the sites used were mountainous, harbor/seaport, mixed thicket/ lush and dense forests, humid climate, rivers, rice fields, and ponds that provide a suitable environment for vector mosquito breeding. *Anopheles* mosquitos' seasonal activity differs in various regions due to environmental conditions²⁴. Also, those collected were identified for species based on their morphological characteristics^{19,21}.

Type of insecticides

Almost all *Anopheles* in this study were reported to be resistant to DDT. Malathion (organophosphate) is still quite effective on *Anopheles sundaicus* 93% in Sri Lanka and *Anopheles superpictus* 100% in Afghanistan. Carbamate are still quite effective for *Anopheles superpictus* 92% in Afghanistan. Pyrethroids were still quite effective with a range of 97–100% in *An. superpictus* (Afghanistan), *An. maculatus* (Lao and Thailand), *An. nivosipes* (Lao and Thailand), *An. philippinensis* (Lao and Thailand), *An. minimus*, *An. kochi*, *An. teselatus* and *An. aconitus* (Lao), *An. karwari* and *An. vagus* (Thailand) and *An. annularis* (Thailand-Myanmar border). The application of chemical insecticides is one of the most critical interventions for malaria control, which included organochlorines (DDT, dieldrin, and BHC), organophosphates (pyrimytophos-methyl and malathion), carbamates (propoxur), and pyrethroids (lambda-cyhalothrin and deltamethrin). These chemicals were used in various forms of application, such as indoor residual spraying (IRS) and insecticide-treated mosquito nets (ITNS) for controlling adult mosquitos. In contrast, organophosphates for larviciding were used in malaria-prone areas²⁵. Actually, the pyrethroids were used in various Asia countries for ITNs and long-lasting insecticidal nets (LLINs). They were also considered the most effective because of their advantages, namely low mammalian toxicity, rapid knockdown activity, and high efficacy against a wide range of insect pests, especially mosquitos²⁵.

Insecticide resistance level frequencies

Resistance to various insecticide, especially to DDT and pyrethroids, was common problem in different malaria vector species³². The multiple resistance to organochlorine, organophosphate and pyrethroid in this study was reported in *An. stephensi* (Afghanistan) and *An. culicifacies* (India). *An. hyrcanus* and *An. barbirostris* (Thailand-Myanmar border) and *An. sinensis*

(China) were multiple resistant to organochlorines and pyrethroids, while *An. subpictus* in Sri Lanka was multiple resistant to organochlorine and organophosphate. In Turkey, *An. superpictus* is multiple resistant to organochlorines, organophosphates and carbamates. This multiple resistance was reported in 14 malaria vector in Asia; these included: *An. stephensi*, *An. superpictus*, *An. culinary*, *An. annularis*, *An. minimus*, *An. hyrcanus*, *An. barbirostris*, *An. vagus*, *An. maculatus*, *An. jamessi*, *An. nivosipes*, *An. philippinensis*, *An. umbrosus*, and *An. sinensis*. Most of the new reports were towards pyrethroid compounds, the only insecticides used for LLINs²⁵. It represents a growing challenge for malaria control and elimination in the future. Using the same insecticide for multiple successive IRS cycles may not be recommended; it is preferable to use a rotation system with different groups of insecticides, including carbamates³³. Rotations should start with the insecticides to which there is the lowest frequency of resistance. In high coverage areas with LLINs, pyrethroids may not be a good option for IRS, as this will add to selection pressure; preferably a rotation system with various types of these groups, including carbamates, should be used³³. The rotation should start with an insecticide that has the lowest resistance frequency. In high-coverage areas with LLINs, pyrethroids were good choices for IRS because this added to the selection pressure. Both LLINs and IRS are the most effective insecticides where the local vectors are endophagic and endophilic. But, when the local vectors primary exophagic and exophilic, these interventions still need an essential level of control³.

Furthermore, an insecticide mixture was a better choice for malaria vector resistance and insecticide resistance management. For example Long-lasting Insecticidal Net (LLIN) incorporating permethrin and a synergist, piperonyl butoxide (PBO), into its fibers in order to counteract metabolic-based pyrethroid resistance of *Anopheles gambiae s.s. mosquitos*³⁴. The efficacy of mixed nets, is because it prevents mosquito bites (function of resistance and physical integrity), and kills mosquitos (function of chemical content and mosquito susceptibility)³⁵. Resistance has been observed in more than 500 insect species worldwide, among which over 50 *Anopheles* species (Diptera: Culicidae) are responsible for the transmission of malaria parasites to humans³⁶. Since monitoring of the resistance was a critical element for implementing insecticide-based vector control interventions, there was a need for periodic surveillance at least once a year or preferably every six months¹³. to strengthen the evidence base for the effectiveness of ongoing vector control interventions¹⁹. A new insecticide, Sumishield (clothianidin, neonicotinoid) was prequalified for indoor residue spraying by the WHO in 2017, could be an alternative in dealing with multiple insecticide-resistant *Anopheles*³⁷

Mortality rates of the *Anopheles* populations

The susceptibility and resistance to insecticides are defined based on testing of vector mortality exposure to discriminatory doses: 1) Susceptibility: an observation of more than or equal to the mortality rate of 98% among vectors tested for resistance provides evidence of clear sustainability; 2) Possible resistance: an initial observations of less than 98% of vector mortality in

Table 5. Insecticide resistance management strategies based on *Anopheles* habitat.

Country	Study location	habitat	Insecticide resistance strategies	Reference
Afghanistan	Nangarhar, Laghman, Kunar, Ghazni, and Badakhshan	Rice field, river stream, ponds, and water puddle	Establishing a management plan for insecticide resistance, and monitoring this situation in all malaria-endemic provinces.	20
India	Madhya Pradesh	Forest	Resistance management strategy by appropriate rotation of different insecticides, including carbamates and incorporating a synergist with synthetic pyrethroids for treating mosquito nets for the control of malaria vectors in these areas. Periodical monitoring of susceptibility/resistance status of different insecticides.	8, 19, 21, 22
	Assam-Meghalaya border area, northeast India	Forest, ponds irrigation		
	Rayagada, Nowrangpur, Kalahandi, Malkangiri and Koraput	Cattle sheds, human dwelling		
	Gadchiroli district	Forest		
Thailand	Chiang Mai-Chiang Dao, Mae Hongson, Phrae	Paddy fields and rivulet	Vector prevention strategies and monitoring insecticide resistance. Achieving universal coverage and proper use of LLIN for all people at risk of malaria. Alternative control tools (e.g., insecticide-treated clothes, spatial repellents, or treated hammocks) adapted to the situation of people's activities are more effective in reducing the malaria burden	17, 23, 24
	Thailand-Myanmar Border	Agriculture		
	Khong Chiam, Sirindhorn, Buntharik, and Nachaluay	Forest and rice field		
Iran	Chabahar Seaport, southeast corner of Iran	Seaport	Biological, chemical, and environmental management. Rotation of insecticide. Monitoring and mapping of insecticide resistance in the primary malaria vector for the implementation of any vector control. Evaluation of the mechanisms and implementation of proper insecticide resistance management strategies.	25, 26
	Sistan and Baluchistan	Coastal		
Lao	Phongsaly, Bokeo, LuangPrabang, Vientiane Pro, Borlikhamxay, Khammouane, Savannakhet, Saravane, Sekong, Attapeu.	Forest, village	Routine monitoring of the insecticide resistance levels and mechanisms to ensure effective malaria control. Use of insecticide with different modes of action, rotation, or combination in the same area.	27
	Hainan Island	Mountainous and ricefield		
China	Shandong Province	Irrigated ricefield, aquatic habitat, and small ponds	Cost-effective integrated vector control programs that are beyond synthetic insecticides. The genetic basis of insecticide resistance to implementing more effective vector control strategies. Monitoring the efficacy of common insecticide and exploring the molecular basis of resistance.	28, 29
	Batticaloa, Puttalam, Trincomalee and Ampara	Coastal and inland		
Turkey	Southeastern Anatolia and the Mediterranean	Agricultural, ponds, stream, and swamps	Effective management of insecticide resistance and monitoring of the status at a regular interval to prevent delay to its development. Integrated vector control strategies including biological, chemical, and physical strategies implemented in a combination	31

bioassay carried out shows possible resistance. After this observation is made, further testing is needed to confirm resistance. Additional tests must be done to determine whether the vector mortality rates are consistently lower than 98% and to understand resistance levels³². All vectors had resistance to DDT with a value below 80%; however, the use of insecticide began to decline gradually over the last few decades and was removed entirely from malaria control in 2000. This decline was due to the perceived adverse effects on the environment and decreased public acceptance for spraying indoor residues²³.

Pyrethroids were the most commonly used insecticides for ITN and IRS, which target indoor transmission and mosquitos that bite in the room²⁸. The mortality rate was <80% for the pyrethroid group in *An. vagus*, *An. culinary*, *An. stephensi*, *An. hyrcanus*, *An. barbirostris*, *An. superpictus*, *An. sacharovi*, and *An. subpictus*. This proved that pyrethroid was less effective. Meanwhile, insecticide resistance was present in malaria vectors in Asia, and the genes spread rapidly throughout the world³⁸. Mosquitoes have two acetylcholinesterase genes (*ace-1* and *ace-2*), but only *ace-1* was found to be significantly associated with insecticide resistance²⁸. High insecticide resistance due to insensitive acetylcholinesterase (AChE) has emerged in genes spread of mosquitoes³⁹. In Africa, sublethal doses of pyrethroids for parasite resistance *Plasmodium falciparum* and *An. gambiae s.s.* can interfere with parasite development in mosquitoes, significantly reducing the proportion of infected mosquitoes and the intensity of infection. This mechanism could enable pyrethroid-treated bed nets to prevent malaria transmission despite increased vector resistance⁴⁰. As resistance genes spread from province to province and country to country, it is of course meaningful and very useful to observe whether and how much this spread is accompanied by an increase in routine reports of malaria incidence as recorded in local health facilities³⁷.

Interventions

Several countries in Asia are implementing an insecticide resistance management (IRM) strategy against malaria vectors following the Global Plan for IRM; this will be more effective with the support of national health system policies and cross-sectoral coordination to achieve malaria-free targets 2030. The use of insecticides to reduce vector populations has become the main strategy for malaria control. Presently, 12 of these insecticides belonging to four chemical classes are recommended by the WHO Pesticide Evaluation Scheme (WHOPES) for IRS⁴¹. The nine insecticides used in Asia which recommended by WHO are Bendiocarb, Propoxur, DDT, Malathion, α -Cypermethrin, Cyfluthrin, Deltamethrin, Etofenprox, and Lambda-Cyhalothrin. Current strategies for controlling malaria vectors mainly include IRS with synthetic DDT/pyrethroids and durable LLINs¹⁴. WHO recommends that these insecticides' susceptibility status needs to be monitored annually¹³. However, the last two decades have seen the use of insecticides everywhere, especially pyrethroids, causing widespread resistance and compromising the effectiveness of vector control⁴². Besides, when this situation is detected, the intensity, biochemical and molecular mechanisms should also be investigated. The accurate information

about the underlying resistance mechanism and its intensity or frequency in the malaria vector turns to update the vector control program and ensure the timely management of insecticide resistance³². Therefore, biochemical and molecular tests are recommended to understand the mechanism of pyrethroid resistance, and there have been several reports about this situation in malaria vectors. However, several control strategies are used to overcome resistance, such as rotation, mixture, using biological control, and integrated vector management²⁶.

Limitations

This study had limitations, such as the dissimilar variables investigated, which produced an incomplete analysis. Only 15 articles from eight countries that correlated with the inclusion criteria from the selected ten years of studies. The data on each country's mortality rate presented only the smallest value, therefore, making it difficult to explore the whole data that needed to make the discussion complete. In some countries, the bioassay test did not use carbamate, even though it was effective for controlling certain types of *Anopheles*.

Conclusion

This review found organochlorine (DDT), organophosphate (malathion), and pyrethroids resistance in several *Anopheles* species with a less than 80% mortality rate. The reports of pyrethroid resistance were quite challenging because it is considered effective in the malaria vector control. Several countries in Asia are implementing an insecticide resistance management (IRM) strategy against malaria vectors following the Global Plan for IRM. Intervention and implementation with optimal resource support are carried out in several Asian countries, including the management plans in selecting insecticides, using a rotation system during interventions in the field, regular monitoring, and integrating vector control based on physics, chemistry, and biology. Several strategies are needed, including management plans in selecting insecticides, using a rotation system during the field interventions, regular monitoring, and integrating vector control strategies based on physical, chemical, and biological methods. All these need to be supported by cross-sector policies and cooperation to achieve the 2030 malaria-free target.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Figshare: PRISMA 2009 checklist for an article entitled Current status of insecticide resistance in malaria vectors in the Asian countries: systematic review. <https://doi.org/10.6084/m9.figshare.13586078>¹⁵.

This project contains the following extended data:

- PRISMA flow diagram of systematic review inclusion and exclusion process

Reporting guidelines

Figshare: PRISMA checklist for 'Current status of insecticide resistance in malaria vectors in the Asian countries: systematic review'. <https://doi.org/10.6084/m9.figshare.1358251712>.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Authors' contributions

DS contributed in designing and conducting the study, and also writing the draft of the manuscript, while DP searched and

extracted the used data from the databases. The authors analyzed, edited, read, and approved the final manuscript in the English language. DS: Funding Acquisition of the financial support for the project leading to this publication.

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Manaswini Dehuri

Department of Veterinary Parasitology, College of Veterinary Science and Animal Husbandry, orissa university of agriculture & technology, Bhubaneswar, India

The scope of the article is good and it is a relevant topic. There are grammatical mistakes and many sentences needs to be rewritten in the article e.g.:

- The 2nd line of introduction needs to be rewritten. In the 2nd paragraph of introduction "mainly" has been misspelt.
- In methods the 6th paragraph may be rewritten for ease of understanding. Last paragraph of methods 'were' is misspelt.
- In results, in the 2nd line " missing" should be deleted. 2nd paragraph of results "From Table 2" needs to be deleted. 5th line, forest "an" to be replaced with 'and'. 3rd paragraph, last line should be deleted. 4th paragraph, 2nd line needs to be re written.

Please check the manuscript thoroughly as there are many spelling and grammatical mistakes.

Statistical analysis (test of significance) ought to be done for Table 3 & 4.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Veterinary Entomology, Acarology and Protozoology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 26 January 2022

<https://doi.org/10.5256/f1000research.78974.r118541>

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Josiane Etang

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Most of the comments made on the previous version of the manuscript have been addressed. However, there is a need for further improvement of the English language through the text.

Thank you for your consideration.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

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Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medical entomology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 01 October 2021

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**Charles M. Mbogo**

Kenya Medical Research Institute-Wellcome Trust Research Program, Nairobi, Kenya

The authors are reporting on insecticide resistance data compiled through systematic review from Asian countries. The purpose of this systematic review was to understand the current status of insecticide resistance among malaria vectors and the implementation of the interventions.

Introduction/Background:

The background information is sound, and the research question is easily identifiable. However, a few minor comments:

- Paragraph 2 --- "The prevention of malaria mainly depends on one class of insecticides, namely pyrethroids; however, the increase in resistance to it reduces this treatment's efficacy". This sentence is not clear because malaria control may be done using the 4 available classes of insecticides and not the pyrethroids unless one is talking about LLINs.
- Paragraph 3 -states that "Vector control is an essential aspect of a program organized to manage the disease transmitted by this type of **organism**". Be specific and state what kind of organism is this.

Methods:

The methodologies applied are appropriate and adequately described. The searching process used was also appropriate. However, the authors indicated that they selected the 15 papers based on several criteria of which one included WHO bioassay protocol on the four major insecticide classes and did not consider any other bioassay protocols such as CDC bottle assay.

Currently, insecticide resistance is measured using WHO bioassay protocol and CDC bottle assay. It is important to check if any of the selected publications had any analysis of resistance including CDC bottle assay. If this is correct, then consider it as it could increase the amount of resistance data.

Results:

The results are coherently described with tables and figures. However, Tables 2, 3, 4, & 5 should have clear and legible descriptions.

- Paragraph 2 ..." From Table 2, the malaria vector was divided into three habitats ...". This

sentence needs to be rephrased to make it clear. How can mosquito vectors be divided into three habitats or what do you mean? The sentence that follows this in the same paragraph should also be rephrased for clarity.

- Paragraph 3 "The entire female Anopheles collected was morphologically identified for their species or complexes using stereomicroscopes and morphological keys" The whole of this paragraph and the next one should be combined and written clearly to convey the necessary message.
- "From 15 papers reviewed, the impregnated with insecticides of DDT (4%)..." Insert the word "papers" before impregnated.
- Paragraph 8 ... "Table 5 shows..." Consider revising this paragraph to make it clear.

Discussion and Conclusion

The discussion highlights the different aspects of the findings on the status of insecticide resistance in different Asian countries. These are partly discussed in relation to the current literature and the status of insecticide resistance in the region. However, more discussions are required on the outcomes on the types, levels, and intensity of insecticide resistance and how multiple insecticide resistance was reported in the diversity of malaria vectors present in the region. Below are a few minor issues that need to be addressed:

- Page 12, Paragraph 1: "This became a challenge for malaria control and elimination, therefore, using the same insecticide for multiple successive IRS cycles is not recommended". Revise this sentence and the entire paragraph to make it clear.
- Page 12, paragraph 2: "...applications against resistible mosquitoes". Which are these mosquitoes?
- Page 12, paragraph 4: "This proved that pyrethroid was less effective. Meanwhile, insecticide resistance was present in malaria vectors in Asia, and the genes spread rapidly throughout the world". This statement is misleading ..what evidence do you have that resistance genes were spreading quickly throughout the world?
- Page 12, paragraph 5: It is important to state some of the 12 interventions mentioned here and their challenges and opportunities they have.

Conclusion: The conclusion is not fully drawn from the analysis of this systematic review?

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.**Reviewer Expertise:** Medical Entomology**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 30 June 2021

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**Josiane Etang**

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² Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Douala, Cameroon

The emergence and spread of *Anopheles* resistance to insecticides is a growing issue, that jeopardizes the effectiveness of currently available core malaria vector control tools, i.e. Long Lasting Insecticidal nets (LLINs) and Indoor Residual Spraying (IRS).

Based on data extracted from 15 original articles selected from four science databases, the authors of this paper came out with a baseline review on malaria vector resistance status in Asia. This resistance concerns 23 anopheline species collected in 8 countries between 2012 and 2019, to 10 insecticides belonging to the four chemical classes mostly used for vector control. Additional information on the ecology and habitat of malaria vectors is also provided. Yet, the authors suggested some resistance management strategies, including the selection of insecticides to be used for vector control, the rotation of the interventions, and integrating vector control methods.

However, as a limitation, the low number and the content of the articles that were eligible for this study (15 papers) made it difficult to thoroughly investigate the geographic and structural distribution of insecticide resistance in target countries, as well as the underlying resistance mechanisms. It appears that the drawn conclusions are partly supported by the results of the review. Furthermore, several issues should be addressed to improve the manuscript:

1. Abstract

- Line one: "remained" may be replaced by "led to"; and "due to" replaced by "which is".
- Line two: The study aims to "review" the insecticide resistance status which was previously

determined.

- Conclusion: I would suggest replacing "complicated" with "challenging".

2. Introduction

- Paragraph 1: please update the situation of malaria, according to the world malaria report 2020.
- Paragraph 2: please add "partly" before "reversible", because there are many other factors that may hinder the reduction of malaria burden apart from insecticide resistance.
- Paragraph 3: It is not clear which type of organism the authors are talking about in the first sentence of this paragraph. At the end of the paragraph, please change the position of "regular" and place it before "monitoring"; i.e. "regular monitoring".

3. Methods

- In the last paragraph, it is said that only papers dealing with the WHO bioassay protocol were considered. Currently, the CDC bottle assay is also used for insecticide resistance testing and monitoring. Adding a separate analysis of resistance data from the CDC bottle assay, if any, could probably increase the amount of resistance data.

4. Results

- Paragraph 1: A map showing the countries where insecticide resistance has been reported and the recorded resistance status for each insecticide used is missing.
- Paragraph 2: Please delete "In several countries" since each species is associated with only one or two countries and not all the countries. Also, it is not clear how a malaria vector can be divided into three habitats; and also which malaria vector the authors are talking about?
- Paragraph 3: Please consider revising the first sentence of this paragraph, e.g. All the female *Anopheles* collected were morphologically identified for their species/complexes...". The last sentence about mosquito processing is also confusing; the authors may consider revising it.
- Paragraph 4: Please include "papers" before "impregnated" and replace "was" with "were".
- Paragraph 5: Please delete "summarized in three resistance classes", this is confusing. The authors may just state that "bioassay results were analyzed according to WHO criteria. Also, the reference N°12 is not specific to WHO bioassay protocol, same as reference n°18; please consider revising the numbering of the references. The reference n°13 is appropriate for this paragraph.
- Regarding the interpretation of the results, the authors should check, which of the WHO protocols they used. In the running WHO protocol which was deriving the revision made in 2018, the criteria for interpretation of bioassay results are different from the criteria presented in this paragraph. In the revised protocol, the resistance threshold is 90%, not 80%.
- Paragraph 6: A mortality rate <97% is wide and also includes confirmed resistance, please specify the lowest mortality rates indicating possible resistance.

- Paragraph 8: The first sentence may be as follows: "Table 5 shows that the insecticide resistance management strategies in several Asian countries are through vector control by environmental, biological, and chemical interventions. The implementation of chemical interventions is through insecticide rotation, monitoring their bioefficacy, mapping, and surveillance of malaria vectors. Malaria eradication relies on..."

5: Discussion

- Here are suggestions for subtitles: Types of insecticides, Insecticide resistance frequencies, Mortality rates of Anopheles populations, Interventions.
- Paragraph 2: Types of insecticides - In the second sentence of the paragraph, please replace "And" with "These chemicals". Also, replace "Currently" with "Actually".
- Paragraph 3: Insecticide resistance frequencies - No need to refer to tables in the discussion.
- The authors may combine the first and the second sentences of this paragraph; e.g. "Resistance to various insecticides, especially to DDT and pyrethroids, was common...vector species. Multiple insecticide resistance was reported in 14 malaria vector species in Asia; these include *A. stephensi*...*A. sinensis*." For the last sentence of this paragraph and the first sentence of the next paragraph, the authors should refer to WHO guidelines for using both LLINs and IRS in specific conditions. Please consider replacing "resistible mosquitoes" with "resistant mosquitoes".
- Paragraph 6: Mortality rates of the *Anopheles* - What is the mortality test? Is it the susceptibility test? The author should consider revising the first sentence of this paragraph. It is not clear how a test can be in a range of 98-100%, 80-97%... etc.
- Paragraph 8: In the second sentence of this paragraph, the authors may replace "interventions belonging to..." with "insecticides belonging to..." and delete "durable" from the next sentence.

The following sentences should also be revised as follows:

- "The accurate information about...tuns...of insecticide resistance".
- "Therefore, biochemical...understand the mechanisms...in malaria vectors".
- "However, several control strategies...used to overcome resistance...vector management".

6. Conclusion

The following sentences should also be revised as follows:

- The reports of pyrethroid resistance were quite challenging, because..."
- "integrating vector control strategies based on physical, chemical and biological methods".

7. Tables

- Table 1. The title of this table may be "Article description" rather than "characteristics".
- Column 3 may be title "year of publication" rather than "publish".
- Table 2: The title of this table may be "Mosquito species and their types of habitat" rather than "sample and location characteristics".
- Table 4. The title of this table may be "*Anopheles* mortality rates in insecticide resistance

bioassays" rather than "Mortality rate of insecticide resistance bioassay in *Anopheles*".

- Table 5: The title of this table may be as follows " Insecticide resistance management strategies".

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Not applicable

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Reviewer Expertise: Medical entomology

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