Impact of Insecticide Resistance on Vector Competence

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The capacity of insects to transmit pathogens is known as vector competence (VC). Evidence indicates that insecticide exposure and resistance increase the risk of pathogen transmission. Under this context, adverse effects such as epidemics in human populations or economic repercussions on crops will increase while current vector control efforts become entirely ineffective. However, studies also point to opposite effects where IR or exposure to insecticides reduces VC. To determine the impact of insecticide resistance (IR) on VC precisely, it is essential to establish reproducible experimental designs to reduce the presence of confusing variables that make the interpretation of results difficult. Therefore, although there is evidence related to the influence of IR on VC, more research is necessary.

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1. Introduction

Insects have a close relationship with humans. They participate in activities that benefit human well-being (i.e., pollination) and exert adverse effects such as those observed in public health, crops, hygiene, and other sectors [1]. On the side of unfavorable impacts, the researchers can highlight the insects' role as vectors of diseases. For example, mosquitoes (i.e., Culicidae), triatomine bugs (Reduviidae), blackflies (Simuliidae), and lice (Pediculidae) affect human health by transmitting arboviruses, parasites, or bacteria [2]. Additionally, aphids, whiteflies, and thrips transmit pathogens to economically important crops [3]. Together, vectors of human and crop pathogens cause considerable economic losses due to human health costs and lower agricultural production [4].

This capacity of insects to transmit pathogens is known as vector competence (VC). This trait defines the intrinsic capacity of an organism to acquire, maintain replication, disseminate, and transmit a pathogen. VC is a complex trait influenced by factors such as the genetic background of hosts and insects, strain and genotype of pathogens, and other aspects associated with environmental variables such as temperature [5][6]. For example, many studies have evaluated the VC of Aedes aegypti. It has been determined that the extrinsic incubation period (the time needed for a mosquito to become infectious) is shorter at higher temperatures [7]. Additionally, bacterial symbionts affect VC by shaping immune responses [8]. Furthermore, Souza-Neto et al. [9], in a systematic review of VC literature in different populations of Ae. aegypti did not find any record of a fully refractory natural population to virus infection; however, there are populations completely susceptible to Zika, dengue, and chikungunya viruses, demonstrating differential regulation of VC.

Studies of VC are heterogeneous (e.g., pathogen challenges performed through intrathoracic injections vs. membrane feeding), and experimental limitations are present (e.g., lack of model animals that mimic human pathogenesis). There are several reports giving a detailed description of past and current knowledge of VC in mosquitoes [9][10][11][12][13][14].

The primary strategy to avoid adverse impacts of insects on public health or agriculture is the use of pesticides. Pesticides are molecules used to destroy, prevent, or repel insects that are a nuisance to humans [15]. Nowadays, various chemicals are applied to control insect populations; according to their structure and synthesis, the diversity of insecticides includes chlorinated hydrocarbon compounds, organophosphates, carbamates, pyrethroids, neonicotinoids, formamidines, and other molecules, plus botanical and microbial agents [16]. The continued use of insecticides has had unintended consequences, particularly the emergence of resistant populations in both human and crop insect vectors. Given many reports on the ineffectiveness of chemical agents in controlling insect populations, the researchers can conceptualize insecticide resistance (IR). This phenomenon is defined as the decrease in the susceptibility of an insect population to a previously effective insecticide caused by its continued use and/or possible cross-selection with other chemical substances, which arises through genetic, physiological, or behavioral changes and is also a hereditary trait [17][18][19].

IR has been described in vectors regarding a broad spectrum of chemical compounds, including organophosphates [20][21][22], among others. Four mechanisms have been determined to reduce the efficacy of pesticides: changes in insect behavior, thickening of the insect cuticle, increased activity of detoxifying enzymes, and modification of the target site [23][24][25]. The more studied IR mechanisms are target site modification and detoxifying enzyme alteration. For example, there is a vast amount of literature concerning mutations in the voltage-gated sodium channel (VGSC), known together as knockdown resistant mutations (kdr mutations, hereafter), as well as mutations in the acetylcholinesterase gene (referred

to as Ace mutations hereafter). These mutations are related to pyrethroid and DDT resistance and organophosphate and carbamate resistance, respectively [26][27]. On the other hand, different enzymes participate in detoxification events leading to metabolic resistance. For instance, mixed-function oxidases are greatly involved in pyrethroid resistance [28][29], along with glutathione S transferases and esterases [30][31]. It has been shown that IR affects current efforts in vector control to prevent the emergence of epidemics of emerging or re-emerging diseases such as chikungunya [32][33]. The same has been observed in pest vectors of important crops such as soybeans and tomatoes [34][35][36].

On the other hand, little is known about the impact of IR on VC. Given the actual scenario in which IR affects vector control, the researchers aimed to systematically synthesize and analyze the research on the effect of IR on VC in vector species that impact human health or crops. It is important to note that the researchers only reviewed research that describes experimental procedures that directly link IR and VC.

2. Effects of Insecticide Exposure on Pathogen Transmission

One key aspect that must be considered while exploring current control efforts' effectiveness is determining if insecticide exposure could impair or enhance VC. It is possible that exposure to sub-lethal doses of insecticides could decrease insects' capacity to acquire a pathogen, limiting infection capacity. As this factor remains to be elucidated completely, a contrary enhancing pattern may be present, as reported by Muturi and Alto [37], Moltini-Conclois et al. [38], and Knecht et al. [39]. In this section, the researchers show evidence supporting either of the two scenarios.

Regarding enhancement of VC after exposure to insecticides, Muturi and Alto [40] found increased viral infection and dissemination of the Sindbis virus in Ae. aegypti when larvae were exposed to malathion. However, heat treatment at 30 °C was also applied to immature stages; results must be interpreted with caution as temperature may influence VC [41]. The same effect was found in Ae. aegypti exposed to Bti. Here, the larval exposure augmented dengue infection and dissemination in two Bti-resistant strains of Ae. aegypti [38].

Insecticide susceptibility could interact with physiological characteristics such as insect age. For example, older Ae. albopictus mosquitoes exposed to sublethal doses of bifenthrin develop higher dissemination viral titers of Zika virus than unexposed old (11–12 days old) and younger mosquitoes (6–7 days old). Remarkably, older mosquitoes exposed to bifenthrin exhibited greater viral dissemination to other tissues outside the midgut, even when compared with younger exposed mosquitoes [39].

On the other hand, studies that show an impairment of VC after insecticide exposure are scarcer. Oral consumption of bifenthrin has been shown to reduce dengue infection rates and body titers (dissemination) at 14 dpi in Ae. albopictus, but no effect was observed at 7 dpi [42]. The same trend was consistently found in An. gambiae s. s. collected in Uganda. Homozygous mosquitoes for the kdr mutation L1014S had a reduction in prevalence and infection intensity by P. falciparum after exposure to deltamethrin in contrast to the unexposed control group [43]. Finally, Hauser et al. [44] determined that exposing insects at the larval or adult stage or both stages to permethrin diminished VC of An. gambiae s. s. for P. berghei.

As reported in the previous section, a neutral trend is found in the relationship between insecticide exposure and VC. Alomar et al. [45] reported that exposure to pyriproxyfen had no impact on the infection, dissemination, or transmission rates of the Zika virus in Ae. aegypti.

In this section, the researchers have aimed to review all information regarding the exposure of insects to pesticides; nonetheless, few heterogeneous studies are published. At the time of conducting this research, only seven studies strictly adhered to the direct exposure of immature stages or adult insects to any pesticide and the further evaluation of any component of VC. Besides the small number of studies, there is variation in experimental settings that limits the researchers' ability to establish clear conclusions about the influence of insecticide exposure on VC. For example, only one study was performed in the Anopheles-Plasmodium association [43]; the remaining were conducted in Ae. aegypti or Ae. albopictus [37][38][39][42][45]. To expand this variation, insecticides used for bioassays were from different toxicological groups possessing different modes of action (malathion, an organophosphate [37]; Bti, a biological insecticide [38]; pyriproxyfen, a juvenile hormone analog [45]; bifenthrin [39][42]; permethrin [44]; and deltamethrin [43]). Three studies focused on insecticide exposure in larvae [40][37][45], while the other four were performed in adults [38][41][42][44]; finally, there is also variation in the pathogen used for infections; two studies involved the dengue virus [37][41] (**Table 1**).

Table 1. Studies aimed at the relationship between insecticide resistance (IR) or exposure to insecticides and vector competence (VC).

Species	Pathogen	Insecticide Exposure	Metabolic Resistance	Target Site Modifications	Phenotypic Resistance	Type of Association	Location	Additional Treatments	Ref
Anopheles gambiae	Plasmodium berghei	DDT	GST		DDT	Positive	Lab		

Species	Pathogen	Insecticide Exposure	Metabolic Resistance	Target Site Modifications	Phenotypic Resistance	Type of Association	Location	Additional Treatments	Ref
An.gambiae s.s.	Plasmodium falciparum			L1014S	Deltamethrin	Positive	Field		
	Plasmodium falciparum	DDT		L1014F	DDT	Positive	Field		
	Plasmodium falciparum			L1014F, G119S	OP, CAR, and PYR-DDT	Negative [1]	Lab		
	Plasmodium falciparum			L1014F, G119S	OP, CAR, and PYR-DDT	Positive [2]	Lab		
	Metarhizium [3] anisopliae			L1014F	PYR	Positive	Lab		
	Beauveria bassiana [3]			L1014F	PYR	Positive	Lab		
	Plasmodium falciparum	Deltamethrin		L1014S		Negative	Field		
	Plasmodium berghei	Permethrin				Negative	Lab	Larval competition	
An.s gambiae s. l.	Plasmodium falciparum	α-Cypermethrin, Deltamethrin, Permethrin		N1575Y, I1527T, L1014F, G119S	PYR	Neutral	Field		
	Plasmodium sp.			L1014F, G119S		Neutral	Field		
	Plasmodium falciparum			L1014F, L1014S		Positive	Lab		
An. funestus	Plasmodium falciparum			L119F-GSTe2		Negative [1]	Lab		
	Plasmodium falciparum			L119F-GSTe2		Positive [2]	Lab		
	Plasmodium sp.			L119F-GSTe2		Neutral	Field		
	Plasmodium sp.			L119F-GSTe2		Positive	Field		
	Plasmodium sp.			A296S (GABA)		Negative	Field		
Culex gelidus	Japanese Encephalitis Virus				Deltamethrin, Malathion	Neutral	Field		
Cx. pipiens	Plasmodium relictum			Ester, AceR		Neutral	Field		
	Plasmodium relictum			Ester, AceR		Neutral	Lab		
Cx. quinquefasciatus	Wuchereria bancrofti		Esterase activity			Negative	Field		
	Wuchereria bancrofti		Esterase activity			Negative	Lab		
	WNV			G119S, Ester	OP	Positive	Lab		
	RVV			G119S, Ester	OP	Neutral	Lab		

Species	Pathogen	Insecticide Exposure	Metabolic Resistance	Target Site Modifications	Phenotypic Resistance	Type of Association	Location	Additional Treatments	Ref
Aedes aegypti	DENV-2	DDT				Neutral	Lab	Heat shock	
	DENV-1	Bti				Neutral	Lab	Larval densities	
	Zika			V1016I, F1534C	PYR	Positive	Lab		
	Sindbis	Malathion				Positive	Lab	Heat treatment	
	DENV	Bti			Bti	Positive	Lab		
	ZIKV	Pyriproxyfen				Neutral	Lab		
	DENV-1		CYP and GST	V1016I, F1534C	PYR	Positive	Lab		
	DENV			V1016I, F1534C		Negative	Field		
Ae. albopictus	DENV-2				Deltamethrin	Negative	Lab		
	Zika	Bifenthrin				Positive	Lab		
	DENV	Bifenthrin				Negative	Lab		
Frankliniella occidentalis	Tomato spotted wilt orthotospovirus				Spinosad	Positive	Lab		
	Tomato spotted wilt orthotospovirus				Spinosad	Neutral	Lab		
Myzus persicae	Potato Virus Y	λ-Cyhalothrin		Ace, M918L	Diethyl carbamates PYR	Positive	Lab		

OP, organophosphates; CAR, carbamates; PYR, pyrethroids. [1] Indicates that the negative influence of IR on VC was detected in the prevalence of infection. [2] Indicates that the positive impact of IR or exposure to insecticides was detected in the pathogen's burden (intensity of infection. [3] They were included to show the relationship between infection susceptibility and IR; these are independent of VC.

3. Impacts of Insecticide Resistance on Pest Vectors in Crops

It has been noted that patterns found in vectors of human pathogens are also present in crop pests. To illustrate this relationship, Wan et al. [66] found that spinosad-resistant Frankliniella occidentalis had higher viral replication, dissemination, and transmission of tomato spotted wilt orthotospovirus (TSWV), contrasting with its susceptible counterpart. These results were obtained only in scenarios where short acquisition periods of the pathogen were evaluated. Regarding life parameters, it is remarkable that resistant F. occidentalis showed a prolonged pre-adult stage, a reduced life span, and lower pupation and sex ratios than its susceptible counterpart. Concerning F. occidentalis IR mechanisms, it has been pointed out that several of these mechanisms resemble those found in human-associated vectors, including decreased penetration of insecticides, detoxifying enzymes, and target resistance. Zhang et al. [70] reported evidence of these similarities, who described genes associated with insecticide resistance using metagenomic approaches and alteration of immune pathways in TSWV-infected F. occidentalis.

Another alteration in VC is observed in Myzus persicae, the peach potato aphid. Here, pyrethroid-susceptible individuals (Type J) displayed less acquisition of potato virus Y in λ-cyhalothrin sprayed leaves than the control (non-sprayed) leaves even three days after spraying. When repeating this experiment using a resistant strain (Type O) characterized by an Ace and a kdr mutation in M918L, the spraying of leaves did not produce a reduction in acquisition of potato virus Y by M. persicae type O. It can be hypothesized that the presence of IR mechanisms affects viral acquisition [68]. In contrast to these findings, no association was determined between IR and VC. Zhao et al. [67] found that, after 48 h, there was no difference in transmission rates between susceptible and spinosad-resistant F. occidentalis individuals. This difference could arise given that IR alters only acquisition events and not the molecular machinery related to the transmission of pathogens [66].

All the studies mentioned earlier were conducted in laboratory settings, and less is known regarding how field variants (e.g., different biotypes) could affect this relationship. Studies conducted in whiteflies (Bemisia tabaci) have reported variations in IR as well as genes related to the transmission of tomato yellow leaf curl virus (TYLCV) and tomato crinivirus (TC) among Middle East-Asia Minor 1 (MEAM 1) and Asia II 1 species. It is important to specify the variation of genes involved in IR, such as acetylcholinesterase like protein and cytochrome P450, proteins acting as target sites for

carbamates/organophosphates and detoxifying enzymes for pyrethroids, respectively [71]. On the other hand, protein variants involved in virus transmission were also detected for TYLCV, such as an aldo-ketoreductase and elicitin-like protein 6, in addition to variants for viral transmission of tomato crinivirus such as 70 Da heat shock protein, AAA-ATPase-like domain-containing protein, alpha-glucosidase, and others [71]. Given this example, it is essential to evaluate how this could enhance or hamper VC in the light of IR. Considering these small number of research advances, the researchers can look at fine-scale variation in the relationship between VC and IR in non-human associated vectors. First, it is apparent that, in controlled situations, IR alters the VC of two vectors of crops [66][68][67]. Second, this alteration is complex and remains to be investigated and expanded to other insect species as well as factors such as immune system interplay and evaluation of individuals exposed to insecticides but with one or several resistance mechanisms (**Table 1**).

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