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UPDATES IN PARASITOLOGY FROM ARGENTINA (A SANCHEZ AND A TOLOZA, SECTION EDITORS)

Global Pattern of *kdr*-Type Alleles in *Musca domestica* (L.)

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Abstract

Purpose of Review Houseflies, *Musca domestica* L., are an important sanitary pest that affects human and domesticated animals. They are mechanical carriers of more than 100 human and animal diseases including protozoan, bacterial, helminthic, and viral infections. Recently, it was demonstrated that houseflies acquired, harbored, and transmitted SARS-CoV-2 (COVID-19) for up to 1 day post-exposure. The most widely used control strategy relays on the application of pyrethroid insecticides due to their effectiveness, low mammalian toxicity, low cost, and environmental safety. The main mechanism of action of pyrethroids is to exert their toxic effects through affecting the voltage-sensitive sodium channel (VSSC) modifying the transmission of the nerve impulse and leading to the death of the insects. Target site insensitivity of the VSSC is due to the presence of single nuclear polymorphisms (SNPs) named knockdown mutations (*kdr*). In this review, we synthetize recent data on the type and distribution of these mutations globally.

Recent Findings Housefly resistance is reported in several countries. Increased applications of pyrethroids to control housefly populations led to the emergence of multiple evolutionary origins of resistance determined by five amino acid substitutions or specific mutations in the VSSC: *kdr* (L1014F), *kdr-his* (L1014H), *super-kdr* (M918T + L1014F), *type N* (D600N + M918T + L1014F), and *1B* (T929I + L1014F). According to the global map obtained, high levels of resistance to pyrethroids are associated with the L1014F mutation found mostly in North America, Europe, and Asia, while the *super-kdr* mutation was mostly found in the American continent. The level of protection conferred by these alleles against pyrethroids was generally *kdr-his* < *kdr* < *Type N* ≤ *super-kdr* ≤ *1B*. The relative fitness of the alleles under laboratory conditions was susceptible ≅ *kdr-his* > *kdr* > *super-kdr* suggesting that the fitness cost of an allele was relative to the presence of other alleles in a population and that the reversion of resistance in a free insecticide environment might be quite variable from one region to another.

Summary An adequate integrated pest management program should consider monitoring susceptibility to pyrethroids to detect early levels of resistance and predict the spread and evolution of resistant phenotypes and genotypes. From this review, the pyrethroid resistance status of housefly population was determined in very few countries and has evolved independently in different areas of the world affecting chemical control programs.

Keywords *Musca domestica* · Pyrethroid resistance · Voltage-gated sodium channel · Fitness cost · Global distribution · *Kdr*

Introduction

The common housefly, *Musca domestica* (L.), is a cosmopolitan pest with sanitary implications for humans and domesticated animals. These insects are widely distributed throughout the world and can be found in every continent due to their synanthropic behavior. They are also one of the most common insects associated with human and animal production environments found in poultry farms, cattle sheds, horse stables, and pig farms. Because these sites hold

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great quantities of manure exposed to both high temperature and humidity, these sites are an ideal environment for houseflies to thrive [1, 2]. This can increase the density of flies that can cause stress to workers and animals and/or reduce the economic value of the products. In both livestock and poultry industry, flies cause irritation in the eyes of animals (keratoconjunctivitis) and induce stress altering production and performance [1].

Health Problems

The problems caused by houseflies involve their ability to be mechanical vectors of a wide variety of pathogens, including those that cause anthrax, typhoid fever, cholera, bacillary dysentery, salmonellosis, polio, hepatitis, paratyphoid, porcine respiratory virus, Newcastle virus and amoebic dysentery, among others [3,4, 5]. Flies pick up infectious agents like enterohemorrhagic *Escherichia coli* and parasites causing shigellosis and viral infections with flu-like symptoms like Newcastle virus, via their mouthparts and their body surface. Moreover, foodborne diseases of microbial etiology are an important cause of morbidity and mortality worldwide and of the 31 foodborne hazards causing 32 diseases, more than 60% can be transmitted by houseflies. Among these infectious diseases, norovirus gastroenteritis causes around 230,000 deaths a year [6].

Moreover, it has been demonstrated that houseflies can mechanically transmit Turkey coronavirus [7]. Recently, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in 2019 in Wuhan, China. This is the causative agent of the coronavirus disease 2019 (COVID-19) pandemic that has spread worldwide and killed more than 6 million people [8]. Balaraman et al. [9] found that *Musca domestica* can mechanically acquire, harbor, and transmit COVID-19 to the surrounding environment for a period of up to 1 day after the exposure. It is difficult to determine economic losses, the annual costs of insecticide use, and high costs of legal settlements against producers in recent decades due to houseflies; for example, these were estimated to be $500 million to 1 billion per year, respectively [10•]. Another important implication are the losses from legal fees and disruptions in production due to complaints of residents from surrounding areas affected by housefly outbreaks [11•]. Houseflies were one of the complaints in the recent 50 million settlements against Murphy-Brown LLC, a subsidiary of Smithfield Foods, for nuisance complaints regarding pork processor and hog producer [10•].

Pyrethroids

The most widely used strategy employed to control houseflies has been the application of insecticides, particularly pyrethroids. The effectiveness, low persistence in the environment, and low mammalian toxicity have made these insecticides the preferred compounds for housefly control [12]. Permethrin was the first pyrethroid employed for the control of houseflies and was approved in either Europe or the USA in the early to mid-1980s for agricultural use first. Registration of other pyrethroid active ingredients followed over the next years. The intensive and regularly use of pyrethroids has led to the development of resistance and consequent field failures in control strategies worldwide [13••]. These insecticides continue to be widely used for housefly control [10•]. The development of resistance rendered success control programs toward inefficient ones with important economic and sanitary implications.

Resistance Mechanisms: Target-Site Mutations on the VSSC

Pyrethroid insecticides are potent neurotoxicants affecting voltage-sensitive sodium channels (VSSCs). VSSCs are integral membrane proteins responsible for the conduction of sodium ions that act by opening or closing the channels. When these channels function correctly, the transmission of the nerve impulse occurs. On the contrary, when this impulse is altered by pyrethroids, several intoxication symptoms (hyperactivity, incoordination, tremors, paralysis, and death) are produced. Two major mechanisms of resistance to pyrethroid insecticides have evolved: (1) selected mutations conferred by a decrease on the affinity of the insecticides in the putative pyrethroid binding pocket on the VSSC leading to a target-site insensitivity [14], (2) and cytochrome P450 monooxygenase–mediated detoxification [15]. The first resistance mutation termed knockdown resistance (*kdr*) was identified in houseflies and mapped in the autosome III [16, 17]. The *kdr* allele is due to a single amino acid change from leucine to phenylalanine at the position 1014 (L1014F) [14]. Then, two other mutations in houseflies were identified: L1014H (*kdr-his*) and M918T + L1014F (*super-kdr*) (Fig. 1a).

All these mutations are distributed globally (Fig. 1b) with variation on their frequency through time and locations [13••, 19••, 20]. When all combinations of these mutations were inserted into the sodium gene of houseflies, and were heterologously expressed in *Xenopus* oocytes and registered by electrophysiological experiments, a reduction in the sensitivity of the VSSC to pyrethroids was reported [21]. Recently, two new alleles named *type N* (D600N + M918T + L1014F) and *1B* (T929I + L1014F) were identified in a housefly population from KS, USA, in 2013 [22•]. The level of protection conferred by these alleles against pyrethroids was generally *kdr-his* < *kdr* < *Type N* ≤ *super-kdr* ≤ *1B* [22•]. The inheritance of resistance was an incompletely recessive trait for *kdr*, *kdr-his*, and *super-kdr*, with the exception of the hybrids of *kdr-his/kdr* that

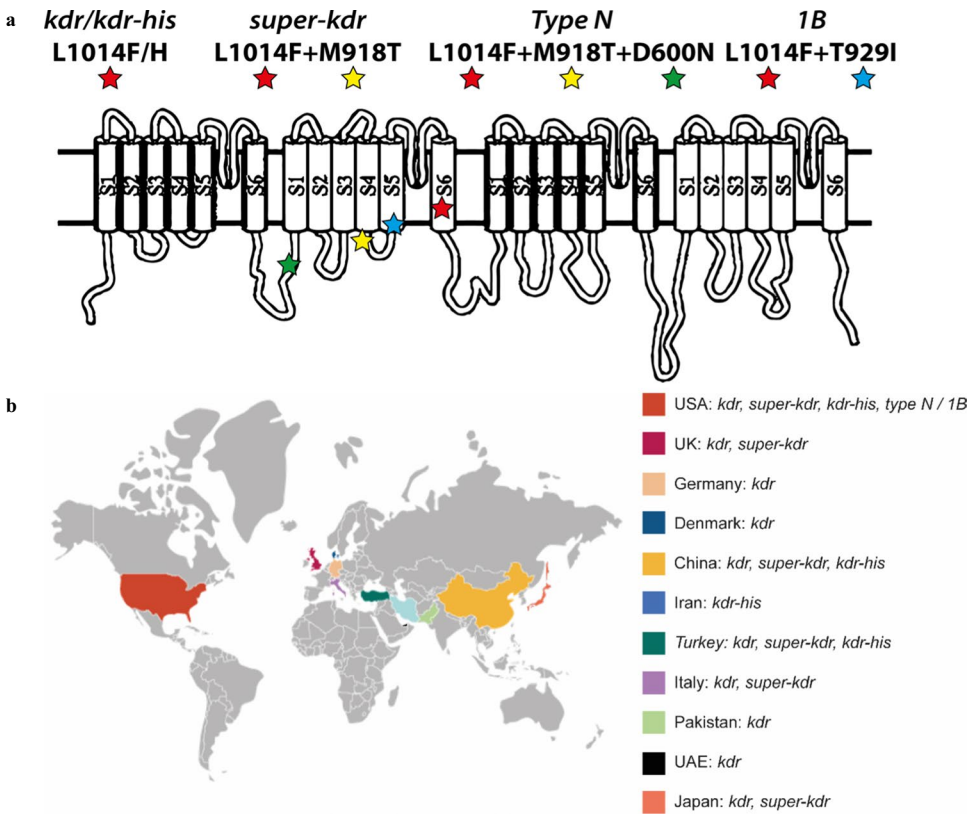


Fig. 1 **a** Location of *kdr* mutations in the voltage-gated sodium channel. Modified from [18]. **b** Distribution of the different *kdr* mutations responsible for pyrethroid resistance in the housefly

showed a generally incompletely to completely dominant inheritance [23].

The goal of this review is to synthetize the available literature regarding pyrethroid resistance in houseflies, the mechanism involved, and the geographical location of their occurrence. In addition, we discuss the evolution of the different patterns related with pyrethroid resistance all over the world.

Methods

Search Strategy and Selection Criteria

A search was conducted in NCBI PubMed following the criteria of all articles published in English language without a year restriction using the search terms *kdr*, *Musca domestica*, and houseflies. Original research and reviews were included. The reference list was meticulously scrutinized for articles not found by the PubMed search. The reference section of each article was searched using the following terms: "Resistance"; "Insecticide"; "*Musca domestica*"; "Pyrethroids"; "*kdr*"; "House Fly". Boolean operator (AND) was used to narrow the search results (Fig. 2).

The first step of the selected studies was the reading of the abstract and if acceptable, it was then fully analyzed. Relevant studies were selected for independent reading of two extra researchers. Causes of rejection were discussed by authors before discarding an article. Reference lists of selected works were reviewed to find works not found in the PubMed search.

Results

In this work, we assessed only selective mutations and overexpression of cytochrome P450 that conferred resistance to pyrethroids in populations of housefly worldwide.

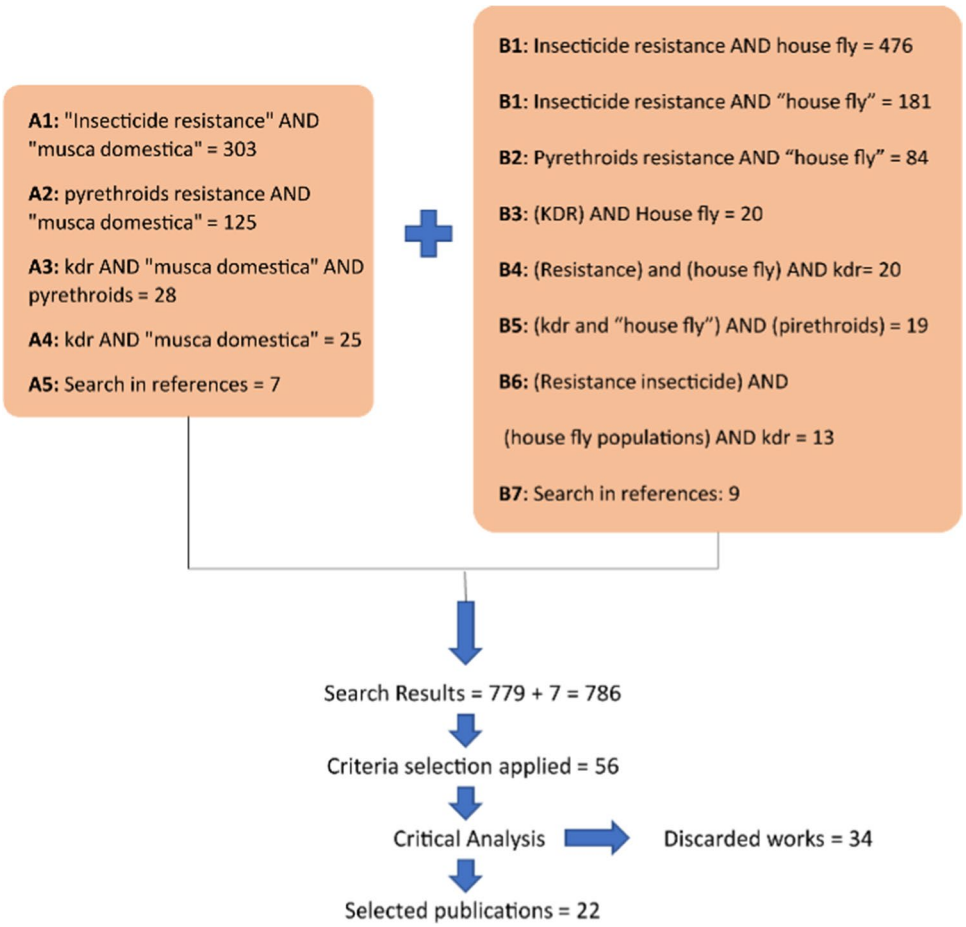
Search Strategy

Target Site Insensitivity (kdr)

After the first broad search, 786 manuscripts were obtained (Fig. 2). Following the selection criteria, 56 manuscripts were selected and 34 discarded after a critical reading which involved the selection of those works that made references to pyrethroid resistance only in populations of *M. domestica* and with *kdr* as their main mechanism of resistance. Thus, we obtained a total of 22 relevant manuscripts.

Different *kdr* point mutations in the voltage-sensitive sodium channel gene showed different levels of resistance: *kdr* (L1014F), *super-kdr* (L1014F + M918T), and *kdr-his* (L1014H). Despite their very local distribution, the recently

Fig. 2 Flow chart diagram



described type N (L1014F + M918T + D600N) and 1B (L1014F + T919I) mutations with *super-kdr*-like resistant levels were also considered.

Geographic Distribution of kdr Mutations

The typical VSSC mutation L1014F responsible for resistance was the *most relevant* in America, Europe, and Asia (Table 1).

This mutation was originally selected for DDT exposure and conferred cross-resistance to pyrethroids in a housefly population [16, 24•]. With the increasing use of pyrethroids (initially permethrin) against *Musca domestica* populations worldwide, different resistance alleles were selected [13••] (Fig. 1b). [13••] [13••] also reports that the resistance level found in several housefly populations collected in the USA of several pyrethroids conferred by *kdr*, *kdr-his*, and *super-kdr* varied in space and time. It is important to mention that most of the resistant studies were from these populations. The resistance levels conferred by the mutations to the 19 tested pyrethroids in congenic strains were as follow: (a) *kdr-his* showed similar levels that ranged from 3.1-fold to tenfold; (b) *kdr* had a variable response that varied from 12-fold to 260-fold; and (c) *super-kdr* showed a more diverse response since for 12 pyrethroids; this mutation conferred an average of 28-fold higher than *kdr* [46]. Meanwhile, for 3 pyrethroids, the resistance levels were 700-fold higher than those of *kdr*. On the contrary, for three multihalogenated benzyl group pyrethroid levels, the levels of resistance were higher for *kdr* than for *super-kdr* [23].

North America

All studies from North America were performed in the USA and two surveys that took place in 2008–2009 and in 2018–2019 possessed the most relevant information about the variation of the levels of pyrethroid resistance in housefly populations [11•, 20].

The 2008–2009 survey conducted in ten locations through the continental United States showed that permethrin resistance was uniformly high, with more than 80% survival at the diagnostic concentrations [11•]. The frequency of VSSC alleles were of: (a) the *kdr* alleles ranged from 0 to 0.59, (b) the *super-kdr* alleles had a variation from 0 to 0.41, and (c) the *kdr-his* allele was found in each state, with frequencies ranging from 0.12 to 0.81. The *Type N* allele was not

Table 1 Knockdown resistance (*kdr*) alleles to pyrethroid insecticides in *Musca domestica*

Country	Mechanism	Marker	References
UK	*kdr*	L1014F	Williamson, 1996 [24•]
	super-kdr	L1014F + M918T	
USA	*kdr*	L1014F	Shono, 2002 [25]
	super-kdr	L1014F + M918T	
USA	*kdr*	L1014F	Liu, 2002 [12]
	super-kdr	L1014F + M918T	
Denmark	*kdr*	L1014F	Huang, 2004 [26]
USA	*kdr*	L1014F	Rinkevich, 2006 [27]
Germany	*kdr*	L1014F	Xu, 2006 [28]
USA	*super-kdr*	L1014F + M918T	Rinkevich, 2007 [29]
Turkey	*kdr*	L1014F	Taskin, 2011 [30]
	kdr-his	L1014H	
USA	*kdr*	L1014F	Rinkevich, 2012 [19••]
China	*kdr-his*	L1014H	
Turkey	*super-kdr*	L1014F + M918T	
USA	*kdr*	L1014F	Wang, 2012 [31]
	kdr-his	L1014H	
USA	*kdr*	L1014F	Scott, 2013 [11•]
	kdr-his	L1014H	
	super-kdr	L1014F + M918T	
USA	*kdr*	L1014F	Rinkevich, 2013 [32]
	super-kdr	L1014F + M918T	
UAE	*kdr*	L1014F	Al-Deeb, 2014 [33]
Italy	*kdr*	L1014F	Mazzoni, 2015 [34]
	kdr-his	L1014H	
	super-kdr	L1014F + M918T	
USA	*kdr*	L1014F	Scott, 2016 [13••]
	kdr-his	L1014H	
	super-kdr	L1014F + M918T	
USA	*kdr*	L1014F	Kasai, 2017 [22•]
	kdr-his	L1014H	
	super-kdr	L1014F + M918T	
	1B	L1014F + T929I	
	Type N	L1014F + M918T + D600N	
USA	*kdr*	L1014F	Sun, 2017 [23]
	super-kdr	L1014F + M918T	
	1B	L1014F + T929I	
	Type N	L1014F + M918T + D600N	
China	*kdr*	L1014F	Pan, 2018 [35]
USA	*kdr-his*	L1014H	Hanai, 2018 [36]
USA	*kdr*	L1014F	Freeman, 2019 [20]
	kdr-his	L1014H	
	super-kdr	L1014F + M918T	
	1B	L1014F + T929I	
Iran	*kdr-his*	L1014H	Kamdar, 2019 [37]
Pakistan	*kdr*	L1014F	Riaz, 2022 [38]

detected and the *1B* allele was found in only one individual [22•]. The susceptible allele was present in all states with frequencies ranging from 0.01 to 0.67. In this study, there was no correlation between the frequency of VSSCs and the geographic distribution (East to West or North to South) of the studied sites.

The survey undertaken in 2018–2019 by Freeman et al. [20] revealed that the frequencies of VSSC pyrethroid alleles varied among sites and changed in 10 years. In terms of the frequency of the pyrethroid resistance alleles, (a) the *kdr* alleles were present in all the analyzed samples and ranged from 0.08 to 0.76, (b) the *kdr-his* mutation varied from 0.12 to 0.28 and was also present in all samples, (c) the *super-kdr* allele ranged from 0.04 to 0.56, and (d) the *1B* allele had a range from 0.01 to 0.45. The susceptible or wild-type allele was only present in one population at a frequency of 0.72. The *Type N* allele was not detected in any population. In addition, all the populations were under Hardy–Weinberg (H-W) equilibrium and there was a significant shift in VSSC allele frequencies.

The *1B* allele was discovered in one population from Kansas in 2013 at low frequency (Kasai et al. 2013), and in 2015 had a frequency of 0.01 in heterozygous individuals (Kasai et al. 2015). Considering that in 3–4 years the frequency raised up to 43.5%, it was suspected that this allele had a potentially lower fitness cost over the *super-kdr* allele [20].

Europe

In Europe, permethrin use led to the development of an additional mutation (M918T) in individuals already harboring the typical kdr mutation (L1014F) [13••, 19••]. This new allele termed as *super-kdr* (M918T + L1014F) allowed for survival at higher doses of the pyrethroid insecticides than those individuals with the *kdr* allele alone. The first report of this new variant was found in a UK field population [24•].

The *kdr* allele (L1014F) remained as the most prominent mutation (around 80%) in populations from Denmark and Italy.

Italy The study conducted by Mazzoni et al. [34] reported the presence of *kdr*, *kdr-his*, and *super-kdr* alleles collected from two sites near Piacenza. The authors reported for the first time the presence of these mutations as responsible for the pyrethroid resistance in Italy. Moreover, an average of 50% of the individuals who carried alleles involved in the survival to pyrethroids.

Denmark A study performed with 14 Danish populations of houseflies showed that the resistant level to pyrethrin + PBO and bioresmethrin + PBO varied from 4 to 29 and from 2 to 98, respectively [26]. In addition, the L1014F allele was detected in all the populations with frequencies ranging from 0.46 to 0.99. Of these, four deviated from the Hardy–Weinberg equilibrium and two had an excess of heterozygotes. In five populations, the resistant levels were above the resistance threshold indicating a failure to control insects in the field, and with *kdr* frequencies that varied from 0.89 to 0.99. In populations with no or low resistance level, the frequency of *kdr* mutations ranged from 0.46 to 0.75 indicating that the *kdr* allele is a fully recessive genetic trait in *Musca domestica*.

Asia

Turkey Houseflies collected in 16 provinces of the Aegean and Mediterranean regions of Turkey showed that *kdr-his* was the most prevalent mutation with an average of 0.20 followed by the *kdr* allele at an average of 0.08. The *kdr-his* frequency between these regions was similar (0.17 and 0.23, respectively). On the contrary, the frequency of *kdr* differed in the Aegean and Mediterranean regions with frequency values of 0.02 and 0.14, respectively [30]. No *super-kdr* allele was detected in any of the studied regions.

Iran Houseflies collected from multiple sites in Urmia showed a very low frequency (0.047) of the L1014H *kdr-his* allele [37]. Other common VSSC mutations of *kdr* and *super-kdr* were not detected in the study. This finding indicated that houseflies from Urmia are susceptible; thus, pyrethroids remain effective to control housefly populations.

China The *kdr* and *super-kdr* alleles were present in a field population of houseflies collected in Beijing in 1983 with a deltamethrin resistance level of 567 [39]. Ten years later, Cao et al. [40] studied several field populations from Beijing and found that the L1014F VSSC mutation had a frequency ranging from 25 to 56%. More recently, a study performed in 2009 by Wang et al. [31] collected houseflies from five sites in China. The resistance level to deltamethrin of this population ranged from 41 to 94. In addition, *kdr* allele was found in only one population at a very low frequency (0.049), while *kdr-his* was widely distributed in heterozygous in all the sites with frequencies ranging from 0.041 to 0.32. All samples had this mutation in heterozygous, and in Guangdong and Shandong, this was in homozygous at a frequency of 2.8% and 9.8%, respectively. In the city of Guangdong where the *kdr* allele was reported, their frequency was lower (0.049) than the *kdr-his* allele (0.11). Thus, this suggests that the *kdr* allele has a more limited distribution than *kdr-his* allele [31]. Despite *super-kdr* previously reported in China [39], this mutation was not detected in another site of China. Housefly populations from China were still dominated by susceptible genotypes and consequently could be managed by the use of pyrethroid insecticides.

Japan The first report of pyrethroid resistance in a field population of houseflies in Japan was in 1984 [41]. Three years later, the *kdr* allele was detected in two populations from Mashiko [42]. After that, Williamson et al. [24•] reported the presence of the *super-kdr* allele in two populations from

Japan. In 1989, again, an invasion of houseflies from Ymenoshima at a dumping site to Tokyo happened were organophosphates were sprayed weekly [25]. The presence of the *kdr-his* allele was not reported.

United Arab Emirates (UAE) The only study conducted in five locations of the United Arab Emirates showed the presence of the *kdr* allele in a frequency ranging from 0.21 to 0.8 [33]. Pyrethroid-resistant homozygous houseflies were present in all the populations with values that varied from 14 to 70%. Only two populations were in Hardy–Weinberg equilibrium.

Pakistan Houseflies collected from seven different locations in Jhang, Punjab, Pakistan, with low resistance levels (1–3) to pyrethroids showed a *kdr* allele frequency of homozygous-resistant and heterozygous genotypes of 28% and 29%, respectively. The *kdr-his* and *super-kdr* alleles were not detected in the studied populations [38].

Origin and Evolution of kdr Pyrethroid Alleles

The selection of *kdr* mutations started in the 1940s with the use of the popular organophosphate DDT and continued in the 1980s with the use of pyrethroids [43]. All over the world, the wide use of pyrethroids (initially it was mainly permethrin) to control housefly populations led to the selection of *kdr* resistance (Fig. 3). In a normal scenario (absence of insecticides), resistance alleles are at a fitness disadvantage because of the fitness cost leading to selection of mutations (amino acid substitutions) that can minimize or reduce this cost [13••]. However, the presence of *kdr* by itself does not necessarily confer protection against field rates of pyrethroids [44] (Kristensen et al. 2001). *Super-kdr* allele was first detected in Denmark and in China, in 1982 and 1983, respectively [13••]. This allele was later detected in the USA in 2003–2004 in New York and Florida [11•, 32]. On the other hand, *kdr-his* was first detected in 1998 in houseflies from Alabama and subsequently in other locations of the USA, Turkey, and China [11•, 12, 13••, 27]. Hence, the use of pyrethroids for the control of housefly populations worldwide resulted in the evolution of different resistance alleles of polygenic trait across the globe [13••] (Fig. 3).

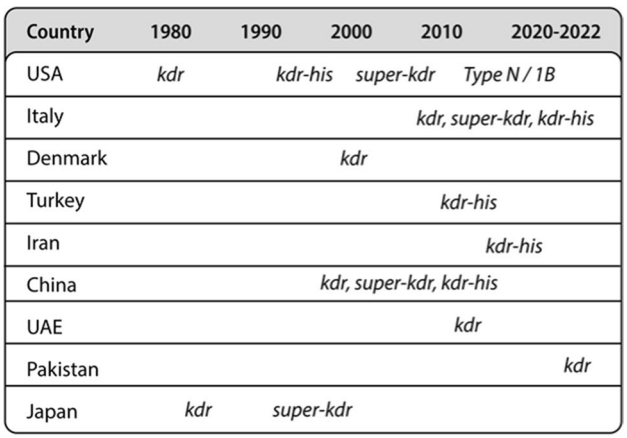


Fig. 3 Timeline evolution of the pyrethroid resistance *kdr* alleles across the world

Phylogenetic analyses of VSSC haplotypes in housefly populations from the USA, Turkey, and China suggested multiple evolutionary origins of *kdr*, *kdr-his*, and *super-kdr* [19••]. Moreover, Rinkevich et al. [19••] found there have been a minimum of two independent origins of *kdr* (L1014F), multiple origins of *kdr-his* (L1014H), and a sequential progression of *super-kdr* (M918T + L1014F) from *kdr*. In mosquitoes *Anopheles gambiae*, it was reported that resistance alleles evolved once and rapidly spread across a large geographic area [45]. This has led to support the hypothesis of the multiple origin of *kdr-type* resistance alleles as a consequence of (1) independent mutational events in different geographic sites and restricted gene flow and (2) geographic selection mosaic, in which alleles from different populations were selected against [19••, 27].

The evolutionary origin and maintenance of pyrethroid resistance alleles within a population are affected by several and non-exclusive factors: the mutation rate, the intensity of selection for and against those alleles (fitness costs), the relative mobility (from farm sites to human settlements), and the inherited trait (dominant or recessive) [19••]. In most of the reports that found a multiple origin of the insecticide resistance, it was inherited as a recessive or incomplete dominant trait [19••, 45]. In the case where the resistance is fully recessive, and once a phenotypically resistant homozygous housefly individual migrates into a new population with no resistant alleles, their progeny would produce only heterozygous offspring, with no resistance. This might explain the detection of resistance alleles in field populations with low levels of resistance to pyrethroids.

Several studies on houseflies have shown that there is a fitness cost for *kdr* alleles in the absence of insecticides [19••]. For instance, it was stated that *kdr-his* (detected in different populations worldwide like the USA, Italy, Iran, Turkey, and China) was commonly present in populations that also have *kdr* and/or *super-kdr*, thus suggesting that it might be the best fit VSSC allele [13••]. In addition, in 2007–2008, the *kdr-his* allele was the most common allele detected in 67% of the states in the USA. Furthermore, over 15 generations in the absence of insecticide use, the *kdr-his* mutation had an overall fitness cost compared with two different susceptible strains [36]. However, the ability to find fitness costs that manifest under laboratory conditions is highly related with the type of stress the housefly populations were exposed. More recently, Freeman et al. [47•]

studied the fitness cost of these mutations from crosses of congenic strains of housefly with known allele frequency over 25 generations under laboratory conditions. They found that the *super-kdr* allele had a significant fitness disadvantage decreasing over time from a frequency of $F_2 = 0.25$ to $F_{25} = 0.05$, and that could not be explained by genetic drift. On the other hand, the frequency of the *kdr* allele was relatively constant over time, whereas there was a slight increase in either the susceptible or the *kdr-his* alleles. Therefore, the relative fitness of the alleles under laboratory conditions was susceptible ≅ *kdr-his* > *kdr* > *super-kdr* as well as in the *super-kdr* allele. Genetic drift was not a relevant potential driver of the observed frequency changes in the susceptible *kdr-his* and *kdr* alleles. This highlighted that the fitness cost of an allele was relative to the presence of other alleles in a population and that the reversion of resistance in a free insecticide environment might be quite variable from one region to another [47•].

Conclusion

There is a considerable variation in VSSC resistance alleles between housefly populations worldwide. Of this, five mutations of multiple origin were reported: *kdr* (L1014F), *kdr-his* (L1014H), *super-kdr* (M918T + L1014F), *type N* (D600N + M918T + L1014F), and *1B* (T929I + L1014F). The present review summarizes the presence and distribution of these pyrethroid-driven mutations in houseflies' populations from several countries. Given the results found in the present work that demonstrate the importance to study these *kdr* mutations in order to carry out an effective chemical control of the housefly, the lack of publications in countries like Canada and continents such as Central/Latin America and Africa is noteworthy. Despite the strong evidence that houseflies have the capacity to develop very high levels of resistance, pyrethroids continue to be widely used against them. The reasons are mainly due to the fitness costs associated with the different resistance alleles leading to a slower establishment of the alleles than was initially predicted. Also, it is expected that pyrethroids might lead to selection for compensatory mutations that would overcome the fitness costs of the resistance alleles in a free pesticide environment. Thus, early detection of their presence in housefly populations is of vital importance and can be used to predict the evolution of resistant alleles in different world regions. Implementation of integrated pest management (IPM) control programs by the combination of biological, mechanical, and cultural strategies is relevant to prevent field control failures and delay detrimental development of pyrethroid resistance.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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