Optimizing Strategic Insecticide Resistance Management Planning in Malaria Vectors

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Additional information is available at the end of the chapter

Abstract

In the past decade, there has been rapid scale-up of insecticide-based malaria vector control in the context of integrated vector management (IVM). But, the continued efficacy of vector control interventions is threatened by the selection of insecticide resistance. Evidence of insecticide resistance operationally undermining malaria vector control programmes is invariably mounting and is resulting in policy changes. Monitoring and management of resistant disease vectors is essential to limit the selection and spread of insecticide resistance and to maintain the effectiveness of vector control. Thus, countries are encouraged to implement pre-emptive insecticide resistance management (IRM) strategies against malaria vectors according to the Global Plan for IRM. However, substantial challenges for implementation exist at country level. The IVM strategy provides a potential platform that could be exploited for enhanced national strategic IRM planning and operationalisation. Nevertheless, significant coordinated response among stakeholders and political commitment is needed for timely and effective policy implementation within the context of a national health system.

Keywords: Malaria vector control, integrated vector, management strategic planning, insecticide resistance management

1. Introduction

Malaria remains a vector-borne disease of major public health significance globally [1]. It is estimated that about 198 million annual cases of malaria and a related 584,000 deaths occur worldwide [2]. Insecticide-based vector control in the context of integrated vector management (IVM) has a long-standing, proven record of preventing, reducing, and eliminating vector-borne diseases [3]. However, its continued efficacy is threatened by the selection of insecticide resistance in disease vectors coupled with the lack of sustainable financial resources [4],

scarcity of requisite skills, and minimal or lack of collaboration between health and other relevant sectors to effectively monitor and manage it [3]. Evidence of insecticide resistance operationally undermining malaria vector control is mounting and is resulting in policy changes [5]. Monitoring and management of resistant disease vectors is essential to limit the selection and spread of insecticide resistance and to maintain the effectiveness of vector control [6]. Nevertheless, substantial challenges for implementation exist at country level. Thus, countries are encouraged to implement pre-emptive insecticide resistance management (IRM) strategies against malaria vectors according to the Global Plan for IRM (GPIRM) [7]. While IVM and IRM are the recommended approaches for combating vector-borne diseases and preventing the spread of resistance respectively, operational experience for both strategies is limited to relatively few countries. However, IVM provides a potential platform that could be exploited for enhanced national strategic IRM planning and deployment. This chapter reviews the distribution, mechanisms, and resistance management strategies in malaria vectors including the challenges experienced in operational settings. A framework of policies and strategies to facilitate the implementation of the GPIRM using the IVM platform is also presented and accentuates coordinated response among stakeholders and political commitment for effective policy execution within the context of national health systems.

2. Literature search strategy

Information sources for this review included all available data and accessible archived documentary records on malaria vectors and insecticide resistance. Structured literature searches of published, peer-reviewed sources using online scientific bibliographic databases were utilised to gather pertinent data. This was conducted via systematic literature search of Library catalogues and online electronic databases, particularly PubMed [8], the WHO Library Database [9], Google Scholar [10], the African Journals Online, the Armed Forces Pest Management Board [11], and the research for life databases (AGORA, ARDi, HINARI, and OARE) were used to search for relevant literature. All digital electronic database searches for peer-reviewed, published work used a combination of key search terms: 1) *Anopheles* malaria vectors complex and one of the following terms; 2) insecticide resistance; 3) resistance mechanisms; 4) resistance management; 5) impact of resistance; 6) malaria vector control; and 7) malaria epidemiology. Reference sections of all relevant articles were also reviewed to identify more literature. Additional non-peer reviewed literature were examined for information related to the subject. Articles that report biochemical and molecular tools for resistance monitoring were also retrieved. The inclusion criteria considered all manuscripts and publications in English language that report on selection of insecticide resistance in malaria vectors, causes and mechanisms of resistance, vector resistance and the epidemiology of malaria, integrated vector management (IVM), resistance patterns, and the impact in malaria vectors.

3. Classification and distribution of malaria vectors

Mosquitoes belong to the family Culicidae in the order Diptera, class Insecta, phylum Arthropoda [12]. Culicidae is divided into three subfamilies Anophelinae, Culicinae, and

Toxorhynchitinae, and comprises approximately 3,450 recognised species of mosquitoes in 38 genera. The 34 genera are in the subfamily Culicinae, 3 in Anophelinae, and only 1 in Toxorhynchitinae [13]. Malaria vectors belong to the genera *Anopheles* (Cellia) Myzomyia and their global distribution has been recognised in six zoo-geographical regions: Palaearctic, Oriental, Australasian, Afro-tropical, Neoarctic, and Neotropical regions [14, 15]. Globally, about 465 species have been described in the genus *Anopheles* with seven subgenera that vary in species composition, i.e., *Anopheles* (182 species), *Baimaia* (one species), *Cellia* (220 species), *Kerteszia* (12 species), *Lophopodomyia* (six species), *Nyssorhynchus* (39 species), and *Stethomyia* (five species) [16]. However, the species able to transmit parasites that cause human malaria only belong to the subgenera, *Anopheles*, *Cellia*, *Kerteszia*, and *Nyssorhynchus* [17]. Only about 80 species are capable of transmitting malaria, 70 species are vectors of malaria under natural conditions and about 45 are of major significance [13]. The distribution of major vectors of malaria is determined mainly by temperature and the capacity of the air to desiccate the insect [18].

The global distribution of principal vectors of malaria is associated with 12 epidemiological zones of malaria: North America (*An. freeborni* and the *An. quadrimaculatus*), Central America (*An. albimanus, An. Aquasalis, An. pseudopunctipennis, An. argyritarsis,* and *An. darlingi,*), South America (*An. darlingi, An. albitarsis, An. Aquasalis, An. marajoara, An. nuneztovari,* and *An. pseudopunctipennis*), Afro-tropical (*Anopheles gambiae* Giles 1902 and *Anopheles arabiensis* Patton in the *An. gambiae* complex, and *Anopheles funestus* s.s. Giles 1900 in the *An. funestus* complex [19, 20] with *An. merus, An. melas, An. moucheti, An. pharoensis,* and *An. nili* implicated in transmission in localised areas [21, 22]), North Eurasian (*An. atroparvus*), Mediterranean (*An. atroparvus, An. labranchiae, An. messeae, An. sacharovi, An. sergentii,* and *An. superpictus*), Afro-Arabian (*An. arabiensis, An. pharoensis,* and *An. sergenti*), Indo-Iranian (*An. culicifacies* and *An. fluviatilis*), Indo-Chinese Hills (*An. dirus, An. fluviatilis,* and *An. minimus*), Malaysian (*An. campestris, An. donaldi, An. letifer, An. nigerrimus, An. aconitis, An. balabacencis, An. dirus, An. flavirostris, An. leucosphyrus, An. ludlowea, An. maculates, An. minimus, An. subpictus,* and *An. sundaicus*), Chinese (*An. barbirostris, An. lesteri, An. sinensis, An. aconitus, An. annularis, An. balabacensis, An. culicifacies, An. dirus, An. farauti, An. flavirostris, An. fluviatilis, An. koliensis, An. leucosphyrus, An. maculates, An. minimus, An. punctulatus, An. stephensi, An. subpictus,* and *An. sundaicus*), and Australasian (*An. farauti, An. punctulatus s.s.,* and *An. koliensis*) [15, 23]. Notably, malaria vector bionomics and their ecological variations have implications for their control.

4. Insecticides and malaria vector control

The classes of insecticides most commonly used for contemporary malaria vector control include organochlorines, organophosphorus, carbamates, and pyrethroids [24]. The first synthetic organochlorine insecticide to be commercialised, DDT (dichlorodiphenyltrichloroethane), was central to the World Health Organisation (WHO)-led global malaria eradication campaign (1955–1969) [25]. Except in sub-Saharan Africa, this resulted in the elimination of the disease in North America, Europe, and parts of Asia [26]. While agricultural use of DDT has now ceased due to environmental persistence and reduced efficacy against resistant insects, extensive use for malaria control continues as a cost-effective and safe insecticide for

indoor residual spraying (IRS). More recently, pyrethroids have been widely used for malaria control. They are the only class of insecticides recommended by the WHO for impregnation of long-lasting insecticidal bed nets (LLINs) [24] and are also available for IRS. Pyrethroids, such as permethrin and deltamethrin, and the pseudo-pyrethroid etofenprox, including DDT and its analogues, share a similar mode of action of targeting the sodium channels of the nerve membranes. Carbamates, such as bendiocarb, share the same mode of action as organophosphates, such as pirimiphos methyl, malathion, and temephos, binding to acetylcholinesterase at the nerve junction [27]. Chlorfenapyr has a different mode of action involving disruption of oxidative phosphorylation and consequently the disruption of the conversion of ADP to ATP in mitochondria [28]. Although insecticides from different chemical classes are available as larvicides (e.g., temephos), the arsenal of insecticides recommended for IRS is limited to four classes only [29]. The selection of DDT resistance in malaria vectors resulted in the declining political and financial support for the Global Malaria Eradication Campaign launched by the WHO [30].

Vector control, personal protection, and community participation are the pillars of WHO strategies for insect-transmitted disease control. IVM has been advocated for as a recommended approach for combating vector-borne diseases in the past decade [31]. IVM is defined as "a rational decision-making process for optimal use of resources for vector control". The objective of vector control is to reduce and/or interrupt transmission of malaria by preventing human contact with malaria-bearing mosquitoes, eliminating breeding sites, killing the mosquito larvae, or reducing the longevity of adult mosquitoes [30]. The use of IRS and LLINs are the mainstream contemporary malaria vector control interventions [32, 33]. The efficacy of these two methods has been evaluated in different epidemiological settings [34] at experimental field trial [35, 36] and community-wide levels [37, 38]. In reducing abundance and infectivity of malaria vectors, these tools reduce overall transmission and protect all individuals within a community [35], albeit with variation in responsiveness amongst vector populations. Presently, there is mounting evidence that combining IRS and insecticide treated nets (ITNs) affords enhanced protection to exposed populations compared to using one method alone [39]. As such, deployment of these interventions together in high malaria risk areas has been advocated [35, 40, 41]. Although these two interventions have been critical in providing community protection, the optimal policy for their co-implementation still remains to be determined. Moreover, the growing resistance of malaria vectors to available insecticides is a major cause for concern and an increasing threat to such essential and effective interventions [24, 42, 43].

In light of the inherent heterogeneity in the responsiveness of malaria vectors to control, the core interventions can be supplemented in specific locations by larval source management (LSM) strategies (e.g., larviciding, biological control, and environmental management) in the context of IVM [44, 45]. Larvivorous fishes or bacterial pathogens such as *Bacillus thuringiensis israelensis* and *Bacillus sphaericus* are examples of biological agents that are used to kill larvae [46]. Temephos is the commonly used chemical larvicide. The environmental methods to prevent malaria include elimination of breeding sites by drainage or by applying locally grown plants. With the selection of resistance, new insecticides, and novel approaches to vector control must be developed. Effective and sustained malaria vector control requires clear commitment from national authorities, including long-term support from funding partners [47]. Several malaria control programmes have fragmentary empirical

evidence to inform policy formulation for rational vector control. For this reason, malaria control programmes are encouraged to adopt the WHO-led IVM strategy [48], which should be an evidence-based decision making process that requires coherent monitoring and evaluation component [49]. This should include routine surveillance of resistance profiles of major malaria vectors and potential resistance mechanisms to facilitate informed decisions and policy changes, such as the incorporation of insecticide resistance management operations into control programmes [29].

5. Insecticide resistance in malaria vectors

The selection of insecticide resistance in malaria vectors has the potential to compromise effective control of vector-borne diseases. Resistance is defined as "the development of an ability in a strain of some organism to tolerate doses of a toxicant that would prove lethal to a majority of individuals in a normal population of the same species" [27, 29]. Alternatively, a resistant phenotype has been defined as an insect that survives a dose of insecticide that would normally have killed it [50, 51]. This heritable change in the sensitivity of a vector population is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that disease vector species [52]. The biological phenomenon is a genetically inherited characteristic that develops as a result of selective effects of the relevant insecticidal compound or its analogue and increases in the vector population [15]. In mosquitoes, genetic and phenotypic resistance results from a mutation or gene duplication leading to the alteration of a normal physiology, morphology, or behaviour of the individual phenotype. In this regard, the sensitivity of the nervous system to the insecticide is reduced or the process of detoxification of the insecticide is enhanced. When an insecticide is applied, susceptible individuals are less likely to survive relative to the resistant individuals. The consequence is the propagation and exponential increase in the frequency of the resistance gene within the population over time [29].

Resistance is a multidimensional biological phenomenon that depends for its development on the interaction of multiple influences [27]. The evolution of insecticide resistance is complex and depends on several genetic, biological, and operational factors [53, 54]. The genetic factors include the intrinsic characteristics of the resistant genes (e.g., mono versus polygenic resistance, dominance, fitness cost, and gene interaction), while the biological factors relate to the life cycle of the insect (e.g., rate of reproduction, number of generation/offspring, and rate of migration and isolation). Behavioural/ecological encompass, migration in and out of exposed population, avoidance of the insecticide, effects of age and natural inducers on degradative enzymes, and endophagy/exophagy. Operational factors concern the treatment itself, including the method and frequency of application, dosage, and residual activity of the insecticides as well as insecticide coverage [55]. Among known and potential factors affecting the evolution of resistance, the operational factors are the only ones open to manipulation by man. Therefore, investigation on the development of resistance should ideally take into account of all these factors.

The level of resistance in insect populations is dependent on the amount and frequency of insecticides used, and the inherent characteristics of the insect species selected. Mosquitoes, for instance, are endowed with all attributes suited for rapid resistance development including high reproductive potentials and short life cycles producing several generations per season with abundant progeny [27, 52]. Mostly resistance in a particular species is considered to occur throughout the control area, but in reality, insecticide resistance can be focal in nature and is very heterogeneous even over very small distances. It often develops within a small part of the population of one species of *Anopheles* and assumes different patterns depending on the type of selection pressure [27]. In Guatemala, sampling sites for *Anopheles albimanus* only a few kilometres apart varied not only by presence or absence of resistance, but also by level of resistance and the mix of mechanisms responsible for resistance [56]. The WHO Global Technical Strategy for Malaria 2016–2030 highlights insecticide resistance as a major obstacle to achieving malaria control targets [57]. The current major emphasis in research into vector resistance is double pronged. The first approach strives towards understanding the molecular mechanisms underlying resistance with the view of developing novel vector-control methods that avoid or minimise resistance problems. The second approach to research involves rational resistance management, which is developing and implementing control methods that mini-mise the likelihood that vectors will evolve strong resistance to important insecticides [58].

6. Methods for detecting insecticide resistance

Information on insecticide resistance is important to inform effective vector control policy formulation. As such, detection and monitoring of insecticide resistance in malaria vectors is crucial and has to be conducted together with other entomological surveys [29]. Insecticide resistance can be detected and investigated at many levels; from dose-related phenotypical observations and genotypic approaches ranging from molecular characterisation of genes conferring resistance and their biochemical products, to the role these gene products play in overcoming the toxic effects of insecticides. In order to detect resistance, one needs to be continually looking for it. Measuring phenotypic resistance using bioassays is the recom-mended initial step in establishing resistance levels before genotyping for target-site and metabolic resistance and biochemical assays [59, 60]. Establishing an effective resistance management plan requires simple assays to monitor and evaluate insecticide resistance and its underlying mechanisms. To this end, different biochemical and molecular approaches have been devised, some of which are amenable for field operations. The contemporary applicable methods for resistance monitoring of field populations of mosquitoes are outlined below:

WHO Diagnostic Assays: A bioassay is used to determine the relationship between a physio-logically active agent and the effect that it produces in a living organism [61, 62]. Bioassays with the dosage or the exposure time as the variable are carried out to test the resistance status of insect populations. The WHO diagnostic assay is a useful and handy approach to detect resistance. Insecticide impregnated filter paper is used as a contact surface for exposed mosquitoes. The assay uses insecticide discriminating dosages twice the LD_{99} that kills 100% of non-blood-fed, adult-susceptible Anopheline mosquitoes of known age [59, 63, 64]. The

demerits associated with the assays include: the assay is only able to detect high levels of resistance, i.e., if more than 5% of insects survive the exposure, with the potential exception of dieldrin bioassays, they cannot monitor resistance gene frequencies accurately; cannot give an indication of the underlying mechanisms of resistance; and cannot be used to predict cross-resistance between insecticides [29]. Therefore, the resistance status detected using bioassays, can then be further studied by looking at the mechanisms responsible for resistance using biochemical and molecular assays.

CDC Bottle Assay: These are similar to the WHO discriminating dose assays. However, the CDC bottle assay relies on time mortality data, which are measures of the time it takes an insecticide to penetrate a vector, traverse its intervening tissues, get to the target site, and act on that site. Mosquitoes are exposed to glass bottle surfaces coated with an acetone- or alcohol-based formulation of insecticides. The advantage of this assay is that the rate of insecticide knock down can easily be scored during the course of the exposure period. It is able to give predictive kdr-type resistance mechanism with rapid acting insecticides, such as pyrethroids. However, caution should be exercised, as metabolic resistance mechanisms are capable of eliciting reduced knock-down phenotype without any concomitant change in sensitivity at the sodium channel target site [65].

Synergists: Synergists are enzyme inhibitors of insecticide detoxification enzymes. The synergists, piperonyl butoxide (PBO) and S, S, S- tributylphosphorotrithioate (DEF) are inhibitors of monooxygenases and esterases respectively [64, 66]. Glutathione s-transferase activity is inhibited by Ethacrynic acid (EA), diethyl maleate (DM), and chlorfenethol (CF). By inhibiting specific detoxification enzymes, insecticide synergists can reduce or eliminate the selective advantage of individuals possessing over-expressed or mutated enzymes [67]. Therefore, they are used to suggest the type of metabolic resistance mechanisms present in insect populations [68]. For example, they are used in bioassays to counteract or inhibit the enzymes responsible for resistance to the insecticide. Some are used in control to reduce the dose or rate of application [64]. For example, piperonyl butoxide is commonly added to pyrethroid-based aerosol formulations to decrease the time to knock down and increase the time to recover from the insecticide.

Biochemical Assays: There are two ways that metabolic enzymes can produce resistance [69]; overproduction of the enzyme, which leads to either increased metabolism or sequestration of the insecticide and an alteration in the catalytic centre activity of the enzyme, which increases the rate of insecticide metabolism by the enzyme. Sequestration occurs when the overproduced enzyme rapidly binds and slowly metabolises the insecticide, therefore preventing it from reaching the target site within the insecticide [70]. With sequestration, the resistance level is proportional to the increase in the quantity of the enzyme produced because of the slow insecticide turn-over rate [70]. Biochemical assays are used to give a first indication of the enzyme system involved in resistance [69]. A number of simple biochemical assays [71] are available to detect increased activity of three enzyme systems, esterases [72, 73], glutathione-S-transferases (GST) [74, 75], and cytochrome P450-dependent monoxygenases (P450s) [76] involved in insecticide metabolism. Many of these assays detect increased enzymatic activity against model substrates in resistant individuals. While simple microtitre plate assays to

measure AChE insensitivity using a carbamate or an oxon analogue of a phosphorothioate insecticide exist [77], the applicability of biochemical assays for the GSTs and P450s are not easily amenable in the field [29].

Molecular Assays: Molecular techniques can be used to detect some well-characterised resistance mechanisms. Most techniques employ the method of polymerase chain reaction (PCR). Mutations in the insecticides' target site lend themselves to detection through simple PCR assays, which can readily be used in many field settings. Allele-specific PCR assays have been developed for three major target sites, the GABA receptors [78, 79], the sodium channels (*kdr*) [80, 81], and AChE. The challenge is to adapt these assays for high-throughput field applications as they have the advantage of detecting heterozygous-resistant individuals that may be missed by other assays [29]. Recent advances in genomics have allowed a much more rapid identification of genes that are up or down regulated in insecticide resistant insects using microarray technology [82]. The detoxification microarray chip, developed for *An. gambiae,* contains all potential insecticide resistance genes. The detoxification chips have been developed for *An. stephensi*, pyrethroid resistant *An. funestus*, and *A. aegypti* [29].

Bioassay data as measured by either the CDC or WHO technique have a common limitation of inability to accurately determine gene frequency or predict the epidemiological impact of resistance [83]. Resistance management requires that resistance is detected at very low frequencies, but the two approaches are not sensitive enough to achieve this. While contemporary techniques diverge in their sophistication and ease of use, there is still a need for approaches to enable measurement of the frequency of different mechanisms of resistance in mosquito populations [29].

7. Insecticide resistance mechanisms

In mosquitoes, resistance is mediated through complex mechanisms, including behavioural and/or physiological changes resulting in insecticide avoidance (reduced contact with insecticide), reduced cuticular penetration (of the insecticide through the cuticle), increased sequestration (i.e., stored in the body where it is not harmful), target site insensitivity (i.e., the target site is altered and not affected by the insecticide), or increased bio-degradation (so that it is detoxified before it reaches the target site) [84], and possible increased excretion. The molecular basis of insecticide resistance has been attributed to the existence of mutations in target site genes or metabolic alterations at the level of the activity of the detoxification proteins [56, 85]. Insecticide resistance mechanisms have a biochemical basis and target-site resistance and detoxification enzyme-based resistance remain the two major forms of biochemical resistance [52, 56]. Alone or in combination, target site resistance, which results from the inability of the insecticide to bind to its target, and metabolic resistance resulting from failure of the insecticide to reach its site of action due to enhanced levels of modified activities of detoxification enzymes, confer various levels of resistance to all classes of insecticides [84]. Though long- and well-recognised, the importance of behavioural and cuticular resistance in malaria vectors has been largely overlooked. While resistance arises through Darwinian

selection in a population, it is often a combination of factors that results in the overall expression of the phenomenon [15]. Thus, gene over-expression, amplification, and structural mutations have been linked to insecticide resistance mechanisms in some insects [84]. Cognizant of detailed elaborations given elsewhere [86], a brief description of the key mechanisms is outlined below:

Target site resistance (also called phenotypic resistance) is based on alterations of amino acids in the site of action where the insecticide is supposed to bind, rendering them less sensitive to the active ingredient [58]. Majority of insecticides used in vector control are nerve poisons and target: the acetylcholinesterase (AChE) that hydrolyses the neurotransmitter acetylcholine in the synapses particularly in carbamates and organophosphates; the sodium channels responsible for raising the action potential in the neurons during the nerve impulses involved in the resistance in organochlorines and pyrethroids; or the c-aminobutyric acid (GABA) receptors responsible for chloride-ion neurotransmission in the nervous system, specific for cyclodienes [87, 88]. Mutations have been observed in neuronal enzymes and receptors, leading to well-defined target site alteration and resistance to chemical insecticides [89]. Knock down resistance (Kdr) occurs due to a single or multiple substitutions/mutations in the para-gated sodium channel gene [29]. In *An. gambiae*, two mutations (Leu-Phe [90] and Leu-Ser [91]) have been identified at the same codon. As this is the target site of DDT and pyrethroids, this mechanism produces cross-resistance to the two insecticide classes. Organophosphate and carbamate insecticides inhibit acetylcholinesterase (AChE). Many insect vectors have developed resistance through structural alterations of this target site [58]. These point mutations may act individually or in combination.

Metabolic resistance, on the other hand, usually involves over-expression/over-production of a complex array of specific enzymes capable of detoxifying insecticides or modifications in the amino acid sequences that cause alterations in the levels and activity of detoxifying proteins [58, 90]. The mechanism of increased detoxification contributes to a decrease in the effective dose of insecticides available at the target site [67]. The overproduction of these endogenous detoxifying enzymes may be achieved via two nonexclusive mechanisms: 1) increase in the gene's copy number of available molecules (by gene amplification or expression activation); or 2) mutation in the enzyme coding portion of the gene, so that its product metabolises the insecticide more efficiently [92], preventing it from reaching its target in the nervous system. Metabolic resistance occurs through increased biodegradation of the insecticide, usually through overproduction of detoxification enzymes such as P450s, GST, and carboxylesterases (EST). The P450 cytochromes primarily metabolises pyrethoids and to a lesser extent, of carbamates and organophosphates, carboxylesterases largely detoxify organophosphate and carbamate and to a lesser extent in pyrethroid resistance [93]. GSTs are involved in the detoxification of a wide range of xenobiotics, including the organochloride insecticide DDT [94]. In *A. gambiae*, metabolic resistance to insecticides can be conferred by elevation in the activity of these three classes of detoxifying enzymes. In contrast, there are few examples in literature regarding insect behavioural changes and tegument alterations.

Behavioural resistance involves behaviour changes in response to prolonged exposure to an insecticide resulting in avoidance and reduced contact with lethal doses of an insecticide [95].

Behavioural resistance does not have the same "importance" as physiological resistance but may be considered to be a contributing factor [96, 97]. It remains unclear whether adaptation of malaria vectors species to insecticidal-based vector control interventions may result from a phenotypic plasticity or from selected behavioural traits [98]. Notably, behavioural resistance is characteristically difficult to quantify [99].

Penetration resistance: Reduced penetration involves changes that decrease the rate of penetration or absorption of insecticide through the insect cuticle or digestive tract linings and confers low levels of resistance [68, 100]. This resistance mechanism is not specific and can affect a broad range of insecticides. Reduced uptake of insecticide, often referred to as cuticular resistance, is frequently described as a minor resistance mechanism. More effort is required to identify the significance of cuticular resistance in phenotypic resistance [86].

The understanding of the development of resistance and the design of novel strategies to manage it and to effectively control disease vectors is greatly owed to the characterisation of genes and the molecular mechanisms involved in insecticide resistance [101]. However, the mechanisms of insecticide resistance are generally far less well-understood. Particularly, the contribution these enzymes make towards pyrethroid resistance and their biochemical relationships with P450-mediated resistance is still unclear [84].

8. Distribution of insecticide resistance

The emergence and spread of insecticide resistance to all four classes of insecticides useful in public health invariably threatens the effectiveness of malaria vector control as most programmes rely heavily on insecticide usage [60]. 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 humans [13, 58]. Globally, resistance to at least one insecticide has been identified in 64 countries with on-going malaria transmission [7]. Currently, 27 countries in sub-Saharan Africa have reported pyrethroid resistance in *Anopheles* vectors [102]. The real figure could very well be higher, as a lack of in-country resistance monitoring prevents accurate assessment [60]. Insecticide resistance is a focal phenomenon and as such is not evenly distributed among vector species and varies markedly from one place to the other. Several platforms are available online with vast information on the distribution of insecticide resistance in malaria vectors such as: Anobase (http://anobase.vector-base.org/ir/), Arthropod Pesticide Resistance Database (http://www.pesticideresistance.org), MARA (http://www.mara.org.za), and IR mapper (http://www.irmapper.com). Persuasive evidence for the presence of resistance in primary vector species to all available insecticides has been presented from Africa, Southeast Asia and India, and South and Central America. Corbel and N'Guessan present a detailed description of the country by country situation analysis of resistance in these regions [86]. A summary is presented below:

In Africa, target-site and metabolic-mediated resistance has been detected in *An. gambiae s.l.* malaria vectors across the continent south of the Sahara. Most of the documented evidence comes from west Africa where pyrethroid resistance is predominant in *An. gambiae s.s.*

compared to *An. arabiensis* [102, 103]. High levels of resistance have also been extensively reported in the two major vectors in Central, East, Austral, and South African countries [104, 105]. Two kdr alleles exist in *An. gambiae s.s.* and *An. arabiensis*, the L1014S gene originally from East Africa [90] and the 1014F gene of west African origin alleles [91]. Both mutations have also been reported to co-exist in Gabon and Cameroon [106] and in Uganda [107]. The western kdr was also detected in Kenya [108], Tanzania [109], and also in Zambia [110, 111]. In pyrethroid-resistant *An. gambiae* s.l. metabolic resistance involving increased levels of P450 has been reported in several countries with CYP6P3 and CYP6M2 genes over-expressed [112, 113]. Most data on resistance in *An. funestus* comes from South African countries where the species seems to be the predominant malaria vector [101]. In *An. funestus*, pyrethroid resistance involving increased activity of P450 monooxygenase and/or GST was demonstrated in Southern Africa [114–116] with over-expressed CYP6M7, CYP6P9a, and CYP6P9b genes [117]. Pyrethroid resistance in *An. funestus* has also been detected in East [118] and West Africa [119, 120]. Recently, the spatial scale of the problem in sub-Saharan Africa was brought to the fore through the IRMapper [105].

Southeast Asia and India insecticide resistance has been detected in the main malaria vector species [87]. In the Mekong region, *Anopheles dirus* s.s. [121] and *Anopheles minimus* s.l. [122]. No kdr mutation has been observed so far in these species [123] and pyrethroid resistance seems to result from increased detoxification by esterases and/or P450 monooxygenases [124]. Esterase-mediated pyrethroid detoxification in both *An. epiroticus* and *An. subpictus* and GST-mediated DDT resistance in *An. subpictus* have been reported [121]. *An. vagus* and *An sinensis* are resistant to pyrethroids with high 1014S kdr alleles [124–127]. The presence of the 1014F allele has been revealed in *An. sundaicus, An. aconitus, An. subpictus*, and *An. vagus* [128] (http://www.itg.be/malvecasia/). In India, *An. culicifacies* s.l. has developed strong resistance to pyrethroids [129], DDT [130, 131], dieldrin/HCH [132], and malathion [131]. Both 1014F and 1014S kdr phenotypes have been detected in pyrethroid and DDT-resistant *An. culicifacies* s.l. [130] and *An. stephensi* [134] with elevated activities of GST in DDT resistance in this mosquito species [135]. *An. annularis, An. subpictus*, and *An. philippinensis* are resistant to pyrethroid, DDT, and/or dieldrin/HCH [135]. In Sri Lanka, metabolic resistance involving carboxylesterases (malathion) or monooxygenases and GSTs (DDT) has been detected in *An. culicifacies* s.l. and *An. subpictus* [136, 137]. In Bangladesh, *An. philippinensis, An. maculatus* s.l., and *An. aconitus* have all developed resistance to DDT [138]. *An. stephensi* and *An. sacharovi* in Iran and Turkey are resistant to DDT and dieldrin [139–141]. While *An. maculatus* s.l. and *An. Aconitus* have developed resistance to DDT in Nepal, *An. stephensi* is resistant to malathion in Pakistan [142].

In Central and South America, the primary malaria vectors are *An. darlingi* and *An. albimanus*. In Mexico, *An. albimanus* exhibits high levels of DDT and pyrethroid-resistance with elevated levels of GST, P450, and esterases, and iAChE-mediated carbamate and organophosphate resistance [143, 144]. In Peru, *An. Albimanus* is resistant to pyrethroids [145]. In Colombia, DDT resistance has been reported in *An. darlingi* [146, 147] and pyrethroid resistance in both *An. darlingi* and *An. albimanus* [148]. In *An. darlingi*, both multi-function oxidase (MFO)- and non-specific esterase (NSE)-based metabolic resistance were reported in a deltamethrin and

DDT-resistant population [149]. *An. Nuneztovari*, a secondary malaria vector, is resistant to organophosphate and pyrethroids [150].

9. Resistance and vector control

Insecticide resistance has been perceived to have the potential to undermine efforts to control vector-borne diseases including malaria [151, 152]. However, the impact of resistance on the ability of malaria control intervention to reduce disease transmission is poorly understood [153]. Insecticide resistance triggers a chain reaction that through deteriorated efficacy leads to vector control failure and disease control failure may be expected [153]. Evidence linking the potential of ITNs increasing phenotypic resistance and kdr frequency [154, 155] that threaten to compromise their effectiveness exists [86]. However, whether these various forms of resistance have an impact on the effectiveness of ITNs in malaria control remains a topic of debate among policy makers and researchers [60]. Conclusive evidence of insecticide resistance impacting on the efficacy of vector control interventions in decreasing disease transmission is by large still absent. However, minimal evidence of an effect of resistance on entomological indicators having an impact on disease transmission exist [60]. The number of studies aimed at evaluating the operational significance of insecticide resistance on epidemiological outcomes of malaria remains nominal. This could be ascribed to multiple confounding factors capable of complicating the interpretation of data. The most available evidence is laboratory or experimental huts-based and harnessing entomological outcomes to assess the impact resistance on mosquito biting rates, blood feeding rates, or insect mortality [153]. Conflicting findings on the impact of resistance on vectorial capacity has been reported with some results indicating an increasing effect [156–160] while others present decreasing outcomes [159, 160].

Mostly, the impact of pyrethroid resistance is not clearly observable in entomological and epidemiological terms. For instance, in areas with detected kdr resistance the distribution of LLINs has been shown to successfully reduce malaria transmission [161]. Insecticide resistance has only been directly implicated in operational control failure of pyrethroids in *An. funestus* in South Africa [162]. In 1996, pyrethroid resistance compromised malaria control in KwaZulu Natal following a switch of IRS insecticides from using DDT to deltamethrin [163]. The reintroduction of IRS with DDT controlled the pyrethroid resistant *An. funestus* population and malaria cases dropped by 91% [164]. In Bioko Island, IRS with pyrethroid had no impact on kdr-mediated resistant *An. gambiae* population, but had significant impact on transmission index and malaria cases [39, 42]. After switching to IRS with a carbamate, the mosquito population declined [42]. In Burundi, programmatic IRS with pyrethroids and ITNs markedly reduced Anopheles density by 82% and transmission intensity by 90% and occurrence of clinical episodes by 43% in children despite high kdr frequencies in *An. gambiae* s.s. [40, 165]. In Côte d'Ivoire, ITN-randomised controlled trials demonstrated a significant reduction on the entomological inoculation rate (55%) [166] and on malaria incidence in children <5 (56%) [167] despite the presence of kdr-based pyrethroid resistance.

The current information gathered across Africa indicates that there is rapid loss of efficacy of most pyrethroids against malarial vectors [109, 168]. In Malawi, pyrethroid resistance did not trigger an operationally significant epidemiological impact on malaria parasite prevalence in children [114]. To compromise insecticide vector control, the level of resistance must be high enough to adversely affect disease transmission [169]. Despite the observed decline of vector abundance after the use of the pyrethroid derivatives [170, 171], the reported loss of efficacy of these widely used insecticides should be taken as a major threat for potential resurgence of malarial transmission in areas where gains have already been achieved against malaria vectors [172]. In many cases, vector control may not be affected by the level of resistance but enhanced surveillance and monitoring would be required [56]. This has refocused attention on the production of chemicals that are efficient and cost-effective [161]. The impact of resistance on the ability of the vector to transmit malaria is underexplored due to the scanty published literature available. However, most studies use kdr alleles frequency as a proxy for resistance due to the lack of molecular markers for alternative resistance mechanisms. This can be misleading if metabolic or other resistance mechanisms are the predominant drivers of the phenomenon. There is a need for additional attention to investigate on evolution and devel-opment of resistance to insecticides by disease vectors and consequently the epidemiological impacts of malaria and other vector-borne diseases [153].

10. Resistance management strategies

The long-term control of vectors is threatened by insecticide resistance, which is occurring at a faster pace than new insecticides are being developed. Pre-emptive action to mitigate the development and spread of insecticide resistance is critical in preserving the limited arsenal of insecticides available for public health [143]. With only four classes of insecticides currently recommended for vector control, implementation of effective resistance management strat-egies remains inevitable [29]. Resistance management can be defined as "the containment of the frequency of resistance genes below an acceptable threshold by means of strategic choices of insecticide, dosage, mode of application, or frequency of use"[173]. The mutant alleles that confer insecticide resistance are generated by random events. In the absence of insecticide selection pressure, resistance management strategies take advantage of the adverse fitness costs of resistance genes, to the insects carrying them. Though generally selected against in the absence of selection pressure, alleles with strong pleiotropic effects increase in frequency when insecticide selection pressure is applied. However, the outcome of resistance management strategies can be affected by dominance status of the trait [29, 143].

Resistance management entails the development and implementation of control interventions that minimise the likelihood that vectors will evolve strong resistance to important insecticides [169]. The aim is to prevent or delay the onset of resistance in populations exposed to an insecticide, or develop management programmes that cause existing resistance in populations to decline, through rotating or alternating insecticides as a resistance management strategy before resistance reaches measurable levels [174]. The use of combined classes of insecticides, rotations of insecticides, or mosaic design has shown to overcome resistance problems

effectively than using a single class of insecticide [175, 176]. Temporal rotation over time of two, or preferably more, insecticide classes with different modes of action applied in an alternating sequence is also based on the assumption that an individual mosquito does not carry two resistant alleles [177]. Rotations are particularly effective if the resistance gene has an associated fitness cost [87] and assumes that if resistance to each insecticide is rare, then multiple resistances will be extremely rare [178]. The "mosaic" approach refers to applications of different compounds against the same insect in spatially segregated locations [55] and aim to preserve susceptibility by spatial restriction of insecticides [7]. Larger scale mosaics have been shown to be effective for the management of pyrethroid resistance in *An. albimanus* in Mexico [143, 179]. An alternative is simultaneous utilisation of a mixture of two or more insecticides of unrelated mode of action, the aim being that resistance will evolve more slowly to both insecticides than if either had been used on its own [180]. Unlike rotations, the effectiveness of mixtures is not directly related to the degree of fitness cost. Mixtures of insecticides require the expected frequency of resistant alleles at two different genetic loci to be low and that individual mosquitoes carrying both alleles are rare [181]. The other approach is through combinations of two vector control tools, such that a mosquito that survives contact with one (e.g., LLIN) is exposed to the other one (e.g., IRS) [182]. The success of combinations in effectively managing resistance depends on the ability to kill the vector despite the existence of resistance by using another intervention or insecticide [183]. However, caution should be exercised not to increase selection pressure by combining insecticides with same mode of action (e.g., avoid pyrethroids for both IRS and LLINs) [86].

Ideally, insecticide resistance management should be undertaken using insecticide-based approaches in conjunction with other non-insecticidal vector control methods, in the context of IVM [3]. However, resistance surveillance is a fundamental step and insecticide susceptibility an indispensable resource of resistance management; it provides baseline data for program planning and insecticide selection before the commencement of control operations, facilitates detection of resistance at an early stage so that timely management can be implemented, and enables continuous monitoring of the effect of control strategies on resistance. Establishing international, multi-disciplinary technical working groups with a clear reporting system and defined responsibilities to facilitate data collation and rational policy transformation is critical for optimal IRM strategies. This would require the presence of a multiplicity of partners with vested interest in insecticide resistance, demand close collaboration and sustained coordination of local and external technical experts, and require good stewardship for them to succeed. Availability of entomological resources provides an ideal opportunity to develop a rational IRM plan underpinned by entomological and epidemiological baseline data to facilitate tracking of spatial and temporal resistance profiles of malaria vectors and evaluating its impact on the efficacy of control interventions. There remains a paucity of evidence on the utility of conventional resistance management strategies (e.g., insecticide rotations, mosaics, mixtures, and combinations) in restoring the susceptibility of malaria vectors. There is also a need for well-designed assessments of the operational impact of combinations of insecticidal and non-insecticidal interventions, including larval source management approaches [87].

11. Operational challenges of insecticide resistance management

The WHO has developed the GPIRM to help member states mitigate the development and spread of resistance [7]. However, countries continue to experience substantial constraints for effective deployment. First, there is limited country-level technical resource capacity to support entomological intervention monitoring and evaluation, minimal essential physical infrastructure and logistical resources to support implementation of the plan, including insufficient qualified vector control workforce. Second, gaps in availability of reliable routine monitoring data on vector bionomics, spatial distribution, insecticide resistance, underlying resistance mechanisms, including operational cost of insecticide resistance from epidemiologically representative sites, makes decision-making on resistance management difficult. Third, deficiency in local financial support and sustainability that is threatened by donor dependency. Fourth, timely scale up has been constrained by paucity in coordinating in-country entomological resources, coupled with scepticism surrounding scientific findings by some key national and international implementing and funding organisations. Fifth, skilled international technical assistance is a scarce resource that is overstretched. Sixth, there is limited data on malaria transmission and its correlation to epidemiological indices to guide the targeting of tools and monitoring of their impact. Seventh, poor data quality, management, and willingness to share data by different partners is usually nominal and remain a challenge to documenting insecticide resistance. Generally, there are limited resources and both human and institutional capacity to fill these gaps. However, the potential of IVM provides a window of opportunity that could be exploited for enhanced IRM activities.

Eight countries, Equatorial Guinea, Eritrea, Mozambique, Namibia, Rwanda, South Africa, United Republic of Tanzania, and Zambia, currently have plans of implementing the GPIRM, representing less than 10% of countries that need them. These plans are mainly reactive rather than proactive. Two examples of countries with well-developed plans are Bioko, Equatorial Guinea and Zambia [184]. Despite having good plans, the operational implementation of these plans remains challenging. In Bioko, large-scale LLIN distribution and island-wide pyrethroid-based IRS were conducted before a switch to bendiocarb IRS for eight years, after the detection of kdr-based pyrethroid resistance. Despite kdr, there is evidence that pyrethroids remain operationally effective. Therefore a bendiocarb-deltamethrin annual rotation has been implemented. Pirimiphos-methyl remains a reserve option should this rotation fail, but was considered too expensive to include initially despite the greater treatment longevity. In Zambia, two major vectors (*Anopheles funestus* and *An. gambiae* sensus stricto) are resistant to carbamates and pyrethroids and pyrethroids alone, respectively. A mosaic pattern of insecticide use, driven by the prevalence of the different vectors has therefore been implemented. However, due to the increased cost, coverage has been reduced in a format that may adversely impact disease transmission. Widespread pyrethroid resistance is now a major problem. Getting new active ingredients to market quickly is imperative; large-scale randomised control trials over many years to document efficacy may be unrealistic given the urgency [184].

12. Policy implications of insecticide resistance

To maintain the effectiveness of vector control, countries are encouraged to deploy tools within the context of IVM [3] and to pre-emptively implement suitable IRM strategies against malaria vectors [7]. To help control programmes re-orient to IVM and IRM, strategic direction and technical assistance have been provided for the two approaches. WHO guidance on IVM includes: the Global Strategic Framework for IVM (2004) [3], the Report of the WHO Consultation on Development of a Global Action Plan for IVM [4], Guidance on Policy Making for IVM [185], Core Structure for Training Curricula on IVM [186], Handbook for IVM [187], and Monitoring and Evaluation Indicators for IVM [188]. Yet, only 62% of 113 endemic countries globally and 53% of countries in Africa have national IVM policies and implemented the strategy [184]. Moreover, resistance to at least one insecticide has been identified in 64 countries with on-going malaria transmission [7]. The threat posed by insecticide resistance is highlighted in the GPIRM consisting of five key pillars including: 1) planning and implementation of IRM strategies in malaria-endemic countries; 2) ascertaining proper, timely entomological and resistance monitoring coupled with effective data management; 3) the development of new, innovative vector control tools; 4) filling of gaps in knowledge on mechanisms of insecticide resistance and the impact of current IRM approaches; and 5) making available enabling mechanisms such as advocacy and human and financial resources [7]. The current monitoring of insecticide resistance is inadequate and inconsistent in most settings in which vector control interventions are used. Often, monitoring is performed reactively or ad hoc, depending on local research projects being conducted [7].

With the view to operationalise the GPIRM and optimise resistance monitoring and management, the WHO has developed a framework document for countries to use as a template for their insecticide resistance monitoring and management plans [189]. However, very few countries have established rational IRM strategies and incorporated them into operational IVM-based vector control programmes. Notably, an emergency approach needs to be adopted for IRM with continued advocacy for the GPIRM, similar to that given to Artemisinin resistance management plans is essential. Incorporating other vector-borne disease (i.e., dengue, leishmaniasis, etc.) in the GPIRM and emphasising biological agents, housing improvement, and larviciding as IRM tools is crucial. For example, larviciding uses different classes of chemical insecticides and biological agents with different modes of action to the four classes available for adult vector control and can reduce overall density [184]. The current areas of focus within IVM include: redesigning programs in the context of insecticide resistance response and climate change; reorientation of programs with capacity building and career pathways; encouraging intersectoral work; and IVM in emergency situations [184]. The WHO should address resistance and entomological capacity challenges via support to countries for developing IRM plans, the inclusion of additional mechanism data in the global database, bi-regional training, the development of a global insecticide resistance response plan, and advocacy for action and resource mobilisation. In attempting to control and contain the spread of insecticide resistance, multi-country cross-border reporting systems and proactive planning is also crucial to preserve new tools and should be considered to inform

policy at this level, especially in light of the malaria elimination efforts that many countries have embarked upon [168].

13. Using IVM for optimal IRM implementation

Given the backdrop of escalating resistance and limited vector control tools, as well as global finances that continue to fall short of estimated requirements for malaria control and elimination [2] and restricted entomological capacity [190], there has been some progress in the implementation of the GPIRM [191]. A successful IVM programme includes actions along five key strategic elements that can be harnessed for addressing the pillars of the GPIRM pertinent to country-level strategic planning and implementation. First, Advocacy, social mobilisation, and legislation: to strengthen national insecticide legislation and regulatory mechanisms for their safe and judicious use; ensure insecticide resistance advocacy and communications to effectively target policy makers, implementers, communities, and other stakeholders. Second, Collaboration within the health sector and partners: to establish technical support linkages with insecticide manufacturers and distributors for joint entomological monitoring, insecticide selection, and resistance management; establish partnerships with the ministry of agriculture and ministry of environment for supervision and pesticide management. Third, Capacity building: to identify competencies and staffing levels essential for effective IRM; strengthen human resource capacity through training for entomological resistance monitoring; establish requisite infrastructure including insectaries, entomology labs; establish vector control data management systems. Fourth, Evidence-based decision-making: clarify information needs and data collection methods; establish entomological and epidemiological monitoring plans to help target and evaluate interventions; select insecticides based on local data regarding vector susceptibility and transmission ecology, ensure insecticide selection is based on an IRM plan as outlined in the GPIRM; ensure vector control and vector data collection are completed in a timely and rigorous manner; manage and utilise evidence for decisions and strategy refinement, including annual reassessment. Fifth, Integrated approach: ensure there is adequate, evidence-based guidance on the impact of resistance on malaria vector control interventions; evaluate whether agricultural use and other vector-borne diseases have an impact on resistance; explore additional non-insecticide complementary malaria vector control measures where they may be appropriate [3, 4].

14. Conclusion and way forward

The development and implementation of national Insecticide Resistance Monitoring and Management Plans for malaria control is crucial in operationalising the GPIRM. IVM can be harnessed as a platform for strategic IRM planning. Thus, rational IRM strategies should be an integral part of IVM-based malaria vector control programmes. However, significant coordinated response among stakeholders and political commitment is needed for timely and effective policy implementation within the context of a national health system.

Acknowledgements

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