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Insecticides for Vector-Borne Diseases: Current Use, Benefits, Hazard and Resistance

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1. Introduction

"Insect vector-borne disease" is the term commonly used to describe an illness/or disease caused by an infectious microbe that is transmitted to human by blood-sucking arthropods such as mosquitoes (e.g. malaria, dengue fever, yellow fever, encephalitis, filariasis, West Nile fever and chikungunya), ticks (e.g. Lyme disease), sandflies (e.g. leishmaniasis), tsetse fly (e.g. African trypanosomiasis) and kissing bug (e.g. Chagas disease). These diseases are a global problem, represent a significant threat to human health and cause enormous impact on economic and social life despite considerable national and international control efforts, i.e. malaria alone kills annually around one million peoples (Figure 1 & Table 1) (WHO, 2004; 2010a). It has been well documented by the World Health Organisation (WHO) and in numerous scientific investigations and reports that the use of synthetic insecticides can dramatically reduce the risk of insect-vector-borne diseases, particularly in the case of malaria (Hemingway and Bates, 2003; WHO, 2006a). Current vector control strategies rely heavily on use of insecticides through insecticide-treated nets (ITNs) and indoor residual spraying (IRS) for example. Space spraying constitutes the first line of activity in case of epidemics. Larval control by using insecticides was a success in the past in eradicating malaria in some parts of the world i.e. the Anopheles gambiae Project in Egypt (Shousha,1948) but still do not received much interest in the current strategies.

The current success of IRS and ITNs in reducing malaria, the most deadly vector-borne disease, contributed towards the optimism that elimination of this disease as a public health problem is a feasible objective (Roberts and Enserink, 2007). Substantial international efforts have been made during the last three years enabling distribution to approximately 289 million ITNs in sub-Saharan Africa, enough to cover 76% of the 765 million people at risk of malaria (WHO, 2010). The number of countries that employed IRS as vector control strategy increased from 31 in 2007 to 68 in 2009 (WHO, 2010). Further scale up of IRS and ITNs for

malaria prevention and vector control is occurring throughout the African continent. However, the huge amount of vector control insecticides is used for IRS which represents around 90% of the total quantity of the annual global quantity of insecticide utilized for vector control (WHO, 2010b; Zaim, 2002; Zaim and Jambulingam, 2004; 2007).

Disease	Vector	Disease burden DALYs[1] (thousands) [2]	Deaths (thousands) [2]
Malaria	Anopheles mosquitoes	32 342	838
African Trypanosomiasis	Tsetse flies	1 409	44
Leishmaniasis	Sandflies	1 486	36
Japanese encephalitis	Culex mosquitoes	790	14
Dengue	Aedes mosquitoes	470	13
Chagas disease	Triatomid bugs	342	10
Lymphatic filariasis	Anopheles and Culex mosquitoes	4 879	0
Onchocerciasis	Blackflies	348	0

[1]DALYs, disability adjusted life years.
[2]Adapted from World Health Organization (WHO), projections of mortality and burden of disease, 2004-2030, baseline scenario 2008 (see: http://www.who.int/healthinfo/global_burden_disease/projections/en/index.html).

Table 1. The current burden of vector-borne diseases.

Several insecticides have historically been used for IRS, the first and most well-known being Dichloro Diphenyl Trichloroethane (DDT). According to the World Health Organization position statement (WHO, 2011), DDT is still needed for vector control simply because in some places there is no alternative of equivalent efficacy and operational feasibility. To date, no change has been warranted in the existing WHO recommendations on the use of DDT for IRS. However, the possible adverse consequences of human exposure to DDT cannot be ignored, even with limited evidence, and merit further revision. Yet, pyrethroids (PYs) are the most commonly insecticides used for IRS and also are the only compounds currently approved by the WHO Pesticide Evaluation Scheme (WHOPES) for ITNs (WHO, 2007). Even limited risk assessments undertaken regard to the safety of personal use of ITNs suggested a high margin of safety for PYs (Bomann, 1995; Zaim et al., 2000), we do not know the real consequences of large scale use of PYs on the environment and human health. Indeed in understanding results of these limited risk assessments, it is important to note that even the use of mosquito nets is not new, long term use of long-lasting insecticide-treated bed nets (LLINs), the new generation of ITNs, and in a large scale community-based intervention is a new technology, and some uncertainty remains about the potential for health problems i.e. the potential chronic neuro-behavioural toxicity in humans (Kolaczinski and Curtis, 2004).

Realizing a scaling up of the current vector control methodologies could lead to deploy of tens of millions of doses of insecticides in the form of ITNs and IRS over millions of homes in endemic countries annually. Thus, strategies to ensure a fuller understanding of potential health risks induced by massive use of insecticides and to minimize actual and potential adverse effects on human health are urgently needed. The risks to public health by deployment of DDT or other insecticides must be carefully weighed against the benefits, in

this case the prevention of vector-borne diseases. Moreover, there are strong evidences that more insect vectors species are becoming resistant to the toxic action of these insecticides and through different resistance mechanisms, especially knock-down resistance (kdr) mechanism to DDT and pyrethroids (Rivero et al., 2010; Ranson et al., 2011). The spread of insecticide resistance vertically to new species and horizontally to new countries poses a great danger likely to undermine the contribution of vector control efforts to control of diseases. Based on screening scientific evidences from literature review, discussion in this chapter, will be focused on current status, benefits, resistance and potential hazardous effects on human health of insecticide vectors management.

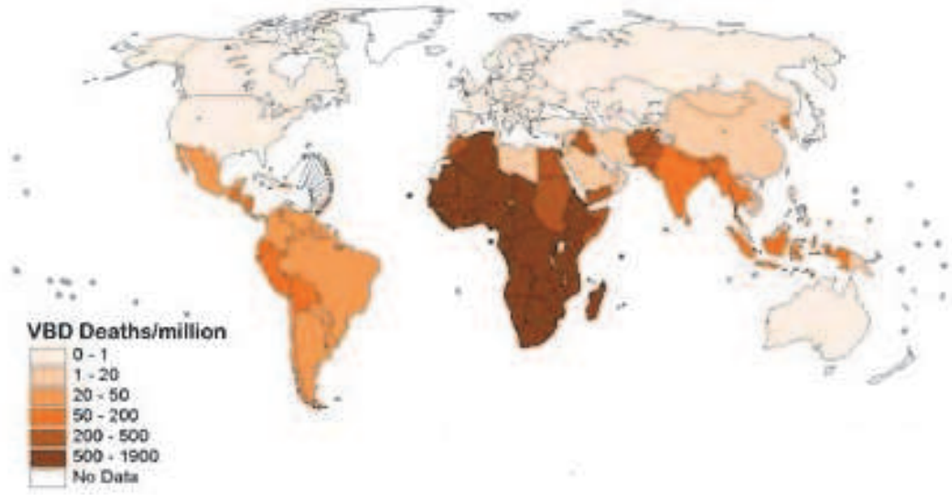


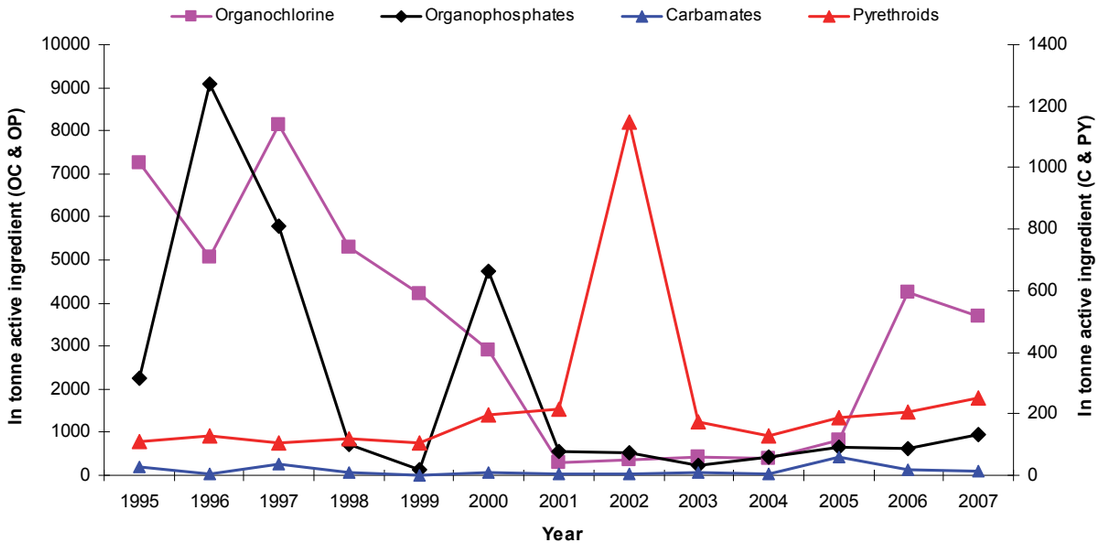
Fig. 1. Death from Vector-Born Diseases (VBD). Source: World Health Organization, Health and Environment Linkages Initiative, available at:
http://www.who.int/heli/risks/vectors/vector/en/index.html

2. Current status of global insecticides use for insect vectors control

On average, about 3962 metric tonnes of active ingredient of organochlorines, 795 tonnes of organophosphates, 16 tonnes of carbamates and 229 tonnes of pyrethroids were reportedly used annually for vector control at the global level during 2006–2007. Compared to previous years of 2000 – 2002, the recent global insecticide use for vector control increased by 333.5% for organochlorines (DDT) and 224% for carbamates. The trend in the global use of insecticides for vector control during 1995 – 2007 is shown in Figure 2.

Compare to 1990s, there is a global decline trend in DDT use, but still on an average, 40,000 tonnes of DDT were used annually during 2006 - 2007 for vector control (Figure 2).This is similar to the annual amount used during the malaria eradication period of 1955–1970. Concerns about the continued use of DDT are fuelled by recent reports of high levels of human exposure associated with IRS amid accumulating scientific evidence on chronic health effects (Sadasivaiah et al., 2007). However, there was a reduction in the use of pyrethroids and organophosphates insecticides. Only 44% and 41% of the total amount of pyrethroids and organophosphates used in 2000-2002 were applied during 2006-2007, respectively (Table 2). Overall, there was a great reduction in use of active ingredient of organochlorines, organophosphates, and carbamates during 2000s compared with 1990s. In

contrast, the use of pyrethroids increased sharply during 2001-2003, corresponding to the period of scaling up of the old generation of ITNs, which required re-treatment by pyrethroids insecticide every six months.



[1] (Data source: Zaim, 2002; Zaim and Jambulingam, 2004; 2006; Ameneshewa et al., 2009).

Fig. 2. Trend in the global use of insecticides for vector control reported to WHOPES, by class of insecticide, 1995–2007.[1]

During 2006–2007, about 90% of the total quantity of all classes of insecticides was reportedly used for IRS for vector control, followed by space spraying (4%), larviciding (3.8%), treatment of mosquito nets (0.3%) and other applications (0.6%).

Year	Insecticide Class[2]	WHO region						
		African	Americas	Eastern Mediterranean	European	South-East Asia	Western Pacific	All regions
2000-2002	OC	307 445	725	0	0	879 761	0	1 187 931
	OP	34 170	358 136	58 988	6 660	1 482 000	6 205	1 946 158
	C	331	2 811	1 481	133	1 237	0	6 993
	PY	2 688	460 940	7 901	1 278	17 257	29 071	519 134
2003-2005	OC	546 909	0	0	0	0	0	546 909
	OP	11 707	367 827	21 148	3 317	24 554	8 686	437 239
	C	20 307	2 681	622	0	1 920	0	24 230
	PY	13 606	91 948	15 375	1 411	9 979	29 553	161 872
2006-2007	OC	755 179	0	0	0	3 206 931	9	3 962 118
	OP	6 403	466 233	52 398	1 620	226 951	41 265	794 868
	C	6 137	781	7 148	1 076	520	0	15 662
	PY	6 616	108 450	26 802	3 228	28 927	54 891	228 913

[1] (Data source: Zaim, 2002; Zaim and Jambulingam, 2004; 2006; Ameneshewa et al., 2009).
[2] OC= Organochlorines exclusively DDT; OP= Organophosphates; C= Carbamates; PY= Pyrethroids.

Table 2. Global use of insecticides for vector control reported to WHOPES, in kg of active ingredient, by class of insecticides and WHO region, 2000–2007.[1]

While the same order of application methods was also reported for 2003–2005, there was a marked increase in the proportion of insecticides used for IRS (from 60%) and a marked decrease in the proportion of insecticides used for space spraying (from 30.7%). There was also reduction in the annual insecticide used for larviciding in 2007 compared with 2000 indicating decrease of interest in relaying on use of these methods for vectors controls (Table 3).

Type of application	Insecticide Class	Amount of insecticide used (kg active ingredient)							
		2000	2001	2002	2003	2004	2005	2006	2007
IRS	OC	2 921 050	291 800	350 941	423 868	389 210	827 648	4 232 505	3 691 730
	OP	4 263 167	184 782	70925	48 312	32 070	91 232	323 706	583 548
	C	9 472	4 007	5 277	6 242	4 417	61 235	17 798	11 761
	PY	96 413	96 402	659 458	82 164	71 183	55 128	122 957	121 912
ITN	PY	43 650	18 253	9 426	15 838	4 694	31 819	6 989	21 412
Larviciding	OP	245 556	112 871	123 659	90 725	89 426	83 136	187 935	189 518
Space spraying	OP	238 929	246 271	324 741	84 243	311 948	473 994	106 643	173 736
	PY	51 090	57 718	56 604	49 675	50 336	98 021	41 233	94 219
Other applications	OP	N.A[2]	N.A	N.A	N.A	N.A	N.A	12 682	10 717
	C	N.A	N.A	N.A	N.A	N.A	N.A	1 019	746
	PY	N.A	N.A	N.A	N.A	N.A	N.A	22 182	10 131

[1] (Data source: Zaim and Jambulingam, 2004; 2006; Ameneshewa et al., 2009).
[2]N.A= Data is not available

Table 3. Recent use of insecticides for vector control reported to WHOPES, in kg of active ingredient, by type of application and class of insecticide, 2000–2007.[1]

The use of organochlorines at global level was reportedly limited only to IRS and the increased reported during 2007 was 126.4% compared with 2000. Except for a report from India on the use of hexachlorocyclohexane (HCH) in 2000, DDT has been the only organochlorines insecticide reportedly used at global level annually for vector control (Zaim and Jambulingam, 2004). This is in agreement with the current approval by WHOPES of insecticides recommended for IRS (Table 4). The organochlorines insecticide had been intensively applied during 1990s and the amount used during this period was more than 5000 metric tonnes of DDT active ingredient, and then decreased to its minimum level (500 metric tonnes) during 2003-2005. Now vectors control activities relayed heavily on the use of pyrethroids insecticides for ITNs and IRS. The use of organochlorines raised slightly again after reintroduction of DDT in 2005 for malaria vector control in several countries of Africa.
Carbamates were mainly used for IRS (94%) and in smaller quantity for other applications (6%) such as dusting, painting and peri-focal treatment. Of the total annual use of organophosphates during 2006-2007, 57% was used for indoor residual spraying, 23.8% for larviciding, 17.7% for space spraying and 1.5% for other applications. While about 55.5% of the total use of pyrethroids was for indoor residual spraying and 30.7% for space spraying, 6.4% was used for treatment of mosquito nets and 7.3% for other applications. In general, the use of

pyrethroids for IRS was increased by 126.5% in 2007 compared with 2000. Interestingly, despite the numerous scaling up and the high coverage achieved, there was a reduction of almost 50% in the annual use of pyrethroids insecticides for treatment of nets in 2007 compared with 2000. This is due to the starting use of the new generation of net, the long lasting insecticidal nets (LLINs) in 2006. LLINs are nets treated in the factory with an insecticide incorporated into the net fabric which makes the insecticide last at least 20 washes in standard laboratory testing and three years of recommended use under field conditions. LLINs are being promoted by WHO and Roll Back Malaria partners as a cost effective and sustainable method for protection against malaria. With LLINs therefore the enormous amount of insecticides requested for retreating old nets is no longer needed.

2.1 Insecticides recommended for IRS

Indoor residual spraying (IRS) is a major intervention for malaria control (WHO, 2006b). There are currently 12 insecticides recommended for IRS, this includes 1 organochlorine, 3 organophosphates, 2 carbamates and 6 pyrethroids insecticides. The only insecticide approved for vector control from organochlorines is DDT. Dosage, toxicity, WHO hazard classification and registration status of DDT and other insecticides recommended for IRS, at U.S Environmental Protection Agency (EPA) are shown in Table 4.

Insecticide compounds and formulations[2]	Class group[3]	Dosage (g a.i./m²)	Oral toxicity for rats (LD50 of a.i. mg/kg)	Duration of effective action (months)	WHO Class[4]	EPA Status[5]
DDT WP	OC	1-2	113	>6	II	Cancelled
Malathion WP	OP	2	2100	2-3	III	Active
Fenitrothion WP	OP	2	503	3-6	II	Active
Pirimiphos-methyl WP & EC	OP	1-2	2018	2-3	III	Active
Bendiocarb WP	C	0.1-0.4	55	2-6	II	Cancelled
Propoxur WP	C	1-2	95	3-6	II	Active
Alpha-cypermethrin WP & SC	PY	0.02-0.03	360	4-6	II	Cancelled
Bifenthrin WP	PY	0.025-0.05	56t	3-6	II	Active
Cyfluthrin WP	PY	0.02-0.05	250	3-6	II	Active
Deltamethrin WP, WG	PY	0.02-0.025	135	3-6	II	Active
Etofenprox WP	PY	0.1-0.3	42	3-6	U	Active
Lambda-cyhalothrin WP, CS	PY	0.02-0.03	56	3-6	II	Active

[1] (Data source: USAID, 2007; WHO, 2009).
[2] CS: capsule suspension; EC = emulsifiable concentrate; SC = suspension concentrate; WG = water dispersible granule; WP = wettable powder.
[3] OC= Organochlorines; OP= Organophosphates; C= Carbamates; PY= Pyrethroids.
[4] II: Moderately Hazardous; III: Slightly Hazardous; U: Unlikely to present acute hazard in normal use.
[5] U.S Environmental Protection Agency (EPA) registration status.

Table 4. WHO recommended insecticides for IRS against malaria vectors.[1]

2.1.1 History of DDT use in IRS

DDT (bis[4-chlorophenyl]-1,1,1-trichloroethane, or dichlorodiphenyl trichloroethane) was the first synthetic pesticide of the modern age. It promised much, but ultimately created widespread concern as an environmental hazard. It was first synthesised in 1874, and its

insecticidal properties were described by Paul Müller in the late 1930s (WHO, 1979). Commercial sales began in 1945, and DDT became widely used in agriculture to control insects, such as the pink boll worm on cotton, codling moth on deciduous fruit, Colorado potato beetle, and European corn borer. The compound was also used in sylviculture and, in a powder form, as a directly applied louse-control substance in people. In the USA, use of DDT rose until 1959 (35 771 tonnes), after which it declined gradually (11 316 tonnes in 1970) (WHO, 1979, ATSDR, 2002; Turusov et al., 2002).

DDT was the first compound used in IRS to protect people against malaria, typhus, and other insect vector-borne diseases. Its first attempt was made by the military personnel in southern Italy in 1944 and in other parts of the world in the final years of World War II (Hays, 2000). Then it was introduced as a vector control measure in civilian populations in Guyana, Venezuela, Cyprus and Sardinia (Giglioli et al., 1974; Gabaldon A, 1983). Large-scale use of DDT for disease vector control was started in 1945 (Hemingway and Ranson, 2000; Webb, 2011). The early successful campaigns of IRS with DDT against malaria vector led to the launch of the Global Malaria Eradication Campaign (GMEC) by WHO in 1955. The GMEC was based on the periodic use of IRS with DDT for 3–5 years to interrupt malaria transmission. However, weak healthcare systems, insufficient administrative, operational constraints, technical capacity, and public reaction to spraying were considered as the major factors contributing to the demise of GMEC. Also, population of anopheline resistant to DDT was primarily responsible for the dwindling political and financial support for GMEC, which ended by 1969 (Litsios, 1996).

2.1.2 Benefit of DDT use

Although GMEC did not achieve its ultimate objective, it was credited with eliminating the risk of the disease for about 700 million persons, mainly in North America, Europe, the former Soviet Union, all Caribbean islands except Hispaniola, and Taiwan (Bruce-Chwatt, 1980). In these regions, incidence of malaria was reduced to zero, or near zero (Curtis and Lines, 2000). In areas with intense and stable transmission (holoendemic to mesoendemic zones) of tropical climates, malaria vectors and prevalence rates were considerably reduced during these projects (e.g., in Cameroon, Kenya, Liberia, Nigeria, Senegal, and Tanzania) (Kouznetsov, 1977; Curtis and Mnzava, 2000; Mabaso et al., 2004). DDT is therefore credited with wholesale suppression and even complete disappearance of vector species such as *Anopheles sergenti* and *Anopheles funestus* from sizeable areas of Egypt, South Africa, Madagascar and Mauritius (Pampana, 1963; Curtis and Lines, 2000). Unfortunately, few African countries participated in the GMEC and even so, the reductions obtained were not sustained after the eradication period because limited resources were devoted to malaria control (Rogan and Chen, 2005; Sadasivaiah et al., 2007).

2.1.3 Environmental risk of DDT use

DDT is a persistent insecticide, does not occur naturally in the environment and is usually found as a white, crystalline, tasteless, almost odorless, and enters terrestrial and aquatic environments through deposition and accidental spillage. Once DDT enters the terrestrial environment, it has a strong affinity for soil and generally remains in the surface layers. As a result of this strong affinity for soil, DDT is quite a persistent pollutant. DDT has a half-life of 15 years, which means if you use 100 kg of DDT, it will break down to 0.39 kg after 120 years (Mader, 1996). This also means that after 100 years, there will still be over a pound of DDT in the environment. DDT has some potential to bio-accumulate in marine life because

it is absorbed by small organisms, such as plankton and fish. It can accumulate to high levels in fish and marine mammals (such as seals and whales), reaching levels thousands of times higher than in water. In these animals, the highest levels of DDT are found in their adipose tissue (ATSDR, 2002). With the publication of "*Silent Spring*" by Rachel Carson in 1962, the safety of DDT for human health and the environment was challenged. This was largely based on the ecological considerations, including persistence in the environment and sufficient bioaccumulation and toxic effects to interfere with reproduction in pelagic birds (i.e., thinning of eggshell). Between 1940 and 1973, estimates indicated that more than 2 million tons of DDT were used in the United States, about 80% of them in agriculture, and some level of resistance was reported in populations of 98 species of economically important insects (Metcalf, 1973). Today, no living organism may be considered free of DDT. It is stored in all tissues, but the highest concentration occurs in fats. The half-life of dichlorodiphenyldichloroethylene (DDE), a primary metabolite of DDT, is about 11 years to disappear from an individual if exposure would totally cease, but that DDE would possibly persist throughout the life span (Smith, 1991; Wolff et al., 2000).

2.1.4 Human health risk from DDT use

Toxic effects of DDT and its analogues have been extensively studied in laboratory animals. People who regularly consumed fish from the American Great Lakes were reported to have higher serum DDE concentrations (median 10 μg/L) than those who did not eat fish (5 μg/L), but they did not show impaired motor function (Schantz et al., 1999), impaired executive and visiospatial function, or reduced memory and learning capacity (Schantz et al., 2001). However, acute exposure to a high dose of DDT can cause death (Smith, 2001). Exposure to DDT or DDE increases liver weight, induces liver cytochrome P450 (CYP) 2B and 3A and aromatase (Li et al., 1995; Sierra-Santoyo et al., 2000; You et al., 2001), and causes hepatic-cell hypertrophy and necrosis (Smith, 2001). In animal, experimental studies confirmed that DDT causes hyperactivity, tremor, and seizures (Rogan and Chen, 2005). The compound is carcinogenic in non-human primates in mice and rats, mainly causing liver tumours (Takayama, 1999; Smith, 2001).

In human, DDT use has been considered generally safe. Doses as high as 285 mg/kg taken accidentally did not cause death, but such large doses led to prompt vomiting. DDT poisoning usually results in paresthesia, dizziness, headache, tremor, confusion, and fatigue (Rogan and Chen, 2005). The compound has been reported to affect neurobehavioral functions and to be associated with premature births (Van Wendel de Joode et al., 2001; Longnecker et al., 2001). Various reproductive and hormonal endpoints have been examined in both men and women, and although associations have been recorded, causal links have not been confirmed. Data from the US Collaborative Perinatal Project showed correlation between preterm delivery and raised concentration of DDE in serum (Torres-Arreola et al., 2003). It has been suggested that maternal exposure to DDT at levels known to occur from IRS could increase preterm birth and shorten duration of lactation (Rogan and Chen, 2005). With few studies mainly conducted in North America, it is difficult to predict causal relationship of DDT exposure to altered preterm delivery or duration of lactation and certainly such findings cannot be extrapolated to other settings like Africa. But if DDT does increase preterm birth and shorten lactation in Africa, it will increase infant mortality. This assumption has been seen by Rogan and Chen, (2005) abrogating the benefit of reducing infant mortality from malaria. However, better understanding on the consequence of the

increase in infant mortality from DDT exposure versus the lives saved from malaria vector control should be a matter for future research (Rogan and Chen, 2005).

Overall human health effects of DDT and DDE most commonly suggested by studies done in North America and Europe are: fertility loss, early pregnancy loss, leukemia, pancreatic cancer, neurodevelopmental deficits, diabetes, and breast cancer (Beard, 2006; Chen and Rogan, 2003; Cox et al., 2007; Eriksson and Talts, 2000; Garabrant et al., 1992; Ribas-Fito et al., 2006; Snedeker, 2001; Venners et al., 2005). In many cases the results have not been consistent between these studies, but nevertheless these accumulating reports bear much concern, particularly in relation to chronic effects. Breast cancer has been most rigorously studied; even though the majority of results showed no causative association with DDT exposure (Brody et al., 2007). This concluded that although extensively studied, there is no convincing evidence that DDT or its metabolite DDE increase risk of cancer to human (Rogan and Chen, 2005).

2.1.5 Ban of DDT use

The concerns about human health and environment led to ban of DDT in Sweden in 1970, the USA in 1972, and the UK in 1986 (Ratcliffe, 1967; Turusov et al., 2002). The global ban on DDT was proposed in 2001 when production and use of DDT are strictly restricted by an international agreement known as the Stockholm Convention on Persistent Organic Pollutants (Stockholm Convention, 2001). The Convention's objective is to protect both human health and the environment from persistent organic pollutants. DDT is one of 12 chemicals identified as a persistent organic pollutant that the Convention restricts. It has been listed in Annex B (Restriction) of the Convention and allowed to be used for disease vector control in accordance with Part II of the annex. Parties must register with the Secretariat to use DDT for disease vector control and comply with specific information collection requirements on the production and use of DDT. In May 2007, 147 countries were parties to the Convention.

2.1.6 Re-introduction of DDT use

When DDT was officially banned in the US in 1972, the WHO reported and concluded that the benefits derived from use of this pesticide were far greater than its possible risks (WHO, 1973). After 35 additional years, these benefits of DDT can be confirmed. In 2000s, several countries in sub-Saharan Africa claimed that DDT was still needed as a cheap and effective means for vector control (Turusov et al., 2002; Rogan and Chen, 2005). The Convention has given an exemption for the production and public health use of DDT for indoor application to insect vector-borne diseases, mainly because of the absence of equally effective and efficient alternatives. According to the WHO Position Statement (WHO, 2011), DDT has several characteristics that are of particular relevance in malaria vector control. Among the 12 insecticides currently recommended for IRS, DDT is the one with the longest residual efficacy when sprayed on walls and ceilings (6–12 months depending on dosage and nature of substrate). In similar conditions, other insecticides have a much shorter residual efficacy (pyrethroids: 3–6 months; organophosphates and carbamates: 2–6 months). Depending on the duration of the transmission season, the use of DDT alternatives might require more than two spray cycles per year, which would be very difficult (if not impossible) to achieve and sustain in most settings. DDT has a spatial repellency and an irritant effect on malaria vectors that strongly limit human-vector contact. Vector mosquitoes that are not directly

killed by DDT but are repelled and obliged to feed and rest outdoors, which contributes to effective disease-transmission control.

There is a general consensus that limited and strictly controlled use of DDT should be allowed for public health purposes (Liroff, 2002). This re-entering of DDT is now supported by key public health organizations and international development agencies, including the WHO, the United States Agency for International Development, and the World Bank (Hemingway and Ranson, 2000). Although the Stockholm Convention of 2001 targeted DDT as one of twelve persistent organic pollutants for phase-out and eventual elimination, it allowed a provision for its continued indoor use for disease vector control. This provision was approved without any objection by approximately 150 national delegations (Stockholm Convention on Persistent Organic Pollutants, 2001). However, still the possible adverse human health and environmental effects of exposure through IRS must be carefully weighed against the benefits of DDT as being low-cost antimalarial tool (Sadasivaiah et al., 2007). WHO has therefore approved the use of DDT under specific condition when "locally safe, effective, and affordable alternatives are not available". WHO points out that DDT spraying is "most effective in reducing the overall malaria burden in unstable transmission areas, regions with marked seasonal transmission peaks and disease outbreaks, and highlands areas" (WHO, 2004).

In general, the past decade has seen a steady increase in commitment to malaria control by the international community (Snow et al., 2008). This has caused a boost in financial and human resources available for implementation of vector control interventions, due to the support of the Global Fund, the World Bank, the U.S. President's Malaria Initiative, and many non-governmental organizations. China, the Solomon Islands, and Vietnam have largely replaced their IRS programs with ITNs during the past decades (Najera and Zaim, 2001). Conversely, the use of IRS is on the increase in Africa, where it has been more difficult to come to grips with malaria because of aspects of vector biology and disease epidemiology. IRS with DDT has become part of the national Roll Back Malaria strategic plan in several countries in Africa (Mabaso et al., 2004; Sharp et al., 2007; Hougard et al., 2002). In India, IRS with DDT has been the mainstay of vector control for more than 5 decades. In general, reports to the WHO showed that the use of DDT for malaria vector control increased substantially among the African nations during 2000–2005 (Table 5), but decreased almost to zero in the Americas due to the signing of the North American Agreement on Environmental Cooperation, a side accord to the North American Free Trade Agreement (Sadasivaiah et al., 2007).

2.2 Pyrethroids compounds used for insecticide-treated nets (ITNs)

2.2.1 History of ITNs

A mosquito net offers protection against mosquitoes, flies, and other insects, and thus against diseases such as malaria, dengue fever, yellow fever, and various forms of encephalitis, including the West Nile virus, if used properly and especially if treated with an insecticide, which can double effectiveness. The fine mesh construction stops many insects from biting and disturbing the person sleeping under net. The mesh is fine enough to exclude these insects, but it does not completely impede the flow of air. A mesh size of 1.2 mm stops mosquitoes, and smaller, such as 0.6 mm, stops other biting insects such as biting midges (no-see-ums). Mosquito netting has a long history. Though use of the term dates from the mid-18th century, use of mosquito nets has been dated to prehistoric times. It is said that Cleopatra, Queen of Egypt, also slept under a mosquito net. Mosquito nets were

Country	2003	2005	2007	Comment
Produce of DDT for vector control				
China	450	490	NA	For export
India	4,100	4,250	4,495	For malaria and leishmaniasis
DPRK	NA	NA	5	> 155 metric tons for use in agriculture
Global production	< 4,550	< 4,740	> 4,500	
Use of DDT for vector control				
Cameroon	0	0	0	Plan to pilot in 2009
China	0	0	0	Discontinued use in 2003
Eritrea	13	15	15	Epidemic-prone areas
Ethiopia	272	398	371	Epidemic-prone areas
Gambia	0	0	NA	Reintroduction in 2008
India	4,444	4,253	3,413	For malaria and leischmaniasis
DPRK	NA	NA	5	> 155 metric tons used in agriculture
Madagascar	45	0	0	Plan to resume use in 2009
Malawi	0	0	0	Plan to pilot in 2009
Mauritius	1	1	<1	To prevent malaria introduction
Morocco	1	1	0	For occasional outbreaks
Mozambique	0	308	NA	Reintroduction in 2005
Myanmar	1	1	NA	Phasing out
Namibia	40	10	40	Long-term use
Papua New Guinea	NA	NA	0	No recent use reported
South Africa	54	62	66	Reintroduction in 2000
Sudan	75	NA	0	No recent use reported
Swaziland	NA	8	8	Long-term use
Uganda	0	0	NA	High Court prohibited use, 2008
Zambia	7	26	22	Reintroduction in 2000
Zimbabwe	0	108	12	Reintroduction in 2004
Global use	> 4,953	> 5,210	> 3,950	

[1]Adapted from van den Berg, 2011.

Table 5. Annual global production and use of DDT (in 103 kg active ingredient) in 2003, 2005, and 2007.[1]

used during the malaria-plagued construction of the Suez Canal (see History of Malaria Control at: http://hub.webring.org/hub/malaria). The mosquito net, while used throughout Asia for centuries, was brought into American mainstream by Col. William Gorgas during the construction of the Panama Canal when thousands of workers, both local

and foreigner, died from the outset of malaria. Mosquito nets treated with insecticides — known as insecticide treated nets (ITNs) or bednets — were developed in the 1980s for malaria prevention (Hung et al., 2002). Newer, longer lasting insecticide nets (LLIN) are starting to replace ITN's in many countries. ITNs are estimated to be twice as effective as untreated nets and offer greater than 70% protection compared with no net (Bachou et al., 2006). These nets are treated using a synthetic pyrethroid insecticide such as deltamethrin or permethrin which improve the protection over a non-treated net by killing and repelling mosquitoes. At least 6 insecticide products are recommended by WHOPES for impregnation of mosquito nets for malaria vector control (Table 6).

Insecticides (Formulations[1])	Dosage[2]	Relevant NOAEL mg (a.i./kg bw/day)	ADI mg (safety factor of 100)	Oral toxicity LD50 (mg/kg/bw)	Dermal toxicity LD50 (mg/kg/bw)
Alpha-cypermethrin (SC 10%)	20-40	1.5	0–0.02	4,932	2,000
Cyfluthrin (EW 5%	50	2	0–0.02	2,100	>5,000
Deltamethrin (SC 1%[3])	15-25	1	0–0.01	>10,000	>10,000
Etofenprox (EW 10%)	200	3.1	0–0.03	>5,0001	>5,000
Lambda-cyhalothrin (CS 2.5%)	10-15	2.5	0-0.02	56	632
Permethrin (EC 10%)	200-500	5	0–0.05	5,000–6,000	4,000–10,000

[1]EC = emulsifiable concentrate; EW = emulsion, oil in water; CS = capsule suspension; SC= suspension concentrate; WT = water dispersible tablet.
[2]Milligrams of active ingredient per square metre of netting
[3] Formulation of WT 25%; and WT 25% + binder (K-O TAB 1-2-3®) are also recommended for this insecticide.

Table 6. WHO recommended insecticide products treatment of mosquito nets for malaria vector control.

2.2.2 Benefit of ITNs use

The use of ITNs has been shown to be an extremely cost - effective method of malaria prevention and are part of WHO's Millennium Development Goals (MDGs). These nets can often be obtained for around $2.50–$3.50 from the United Nations organizations such as WHO and UNICEF, including commercial sources, with additional cost on logistics. Generally LLIN's are purchased by donor groups like the Bill and Melinda Gates Foundation and distributed through in country distribution networks.

Studies on the cost-effectiveness of free distribution concluded on spill over benefits of increased ITN usage (Hawley et al., 2003a). ITNs not only protect the individuals or households that use them, but they also protect people in the surrounding community in several ways (Maxwell et al., 2002). First, ITNs kill adult mosquitoes, the exposure to insecticide directly increases the mortality rate and can therefore decrease the frequency in which a person is bitten by an infected mosquito (Killeen and Smith, 2007). Second, certain malaria parasites require several days to develop within the salivary glands of the vector mosquito. *Plasmodium falciparum*, the parasite responsible for the majority of deaths in sub-Saharan Africa, takes 8 days to mature and therefore malaria transmission to humans does not take place until approximately the 10th day, although would have required blood meals at intervals of 2 to 5 days (Smith and McKenzie, 2004). By killing mosquitoes prior to

maturation of the malaria parasite, ITNs can reduce the number of encounters of infected mosquitoes with humans (Killeen and Smith, 2007). When a large number of nets are distributed in one residential area, their insecticidal additives effect helps to reduce the density of mosquitoes in the environment. With fewer mosquitoes in the environment, the chances of malaria infections are significantly reduced. A review of 22 randomized controlled trials of ITNs (Lengeler, 2004) found that ITNs can reduce deaths in children by one fifth and episodes of *P falciparum* malaria by half. More specifically, in areas of stable malaria "ITNs reduced the incidence of uncomplicated malarial episodes by 50% compared to no nets, and 39% compared to untreated nets" and in areas of unstable malaria "by 62% compared to no nets and 43% compared to untreated nets". As such the review calculated that for every 1000 children protected by ITNs, 5.5 lives would be saved each year.

Despite, the wide acceptance and significant efforts made for scaling up ITNs in Africa (WHO, 2002) questions concerning the long-term acceptability and durability of this strategy are still remaining. First, reductions in all-cause child mortality rates due to short-term effect related to use of nets may not be sustainable, because initial reductions in mortality occur as a result of the combination of reduced malaria transmission and pre-existing partial immunity developed under the formerly higher levels of transmission. After transmission declines and immunity wanes, mortality rates may increase (Molineaux, 1997). Second, pyrethroid resistance in Anopheles mosquitoes might compromise the long-term effectiveness of ITNs in killing mosquitoes (Zaim and Guillet, 2002). Third, it is not clear whether the community will maintain proper use of nets and sustain (adherence) over long periods, particularly when nets are distributed free of charge (Curtis et al., 2003). Fourth, acquired immunity against clinical malaria, a function of the frequency of infections, is delayed as it is developing gradually with time. Therefore, the period during which a child is at risk from clinical malaria might increase where ITNs are used (Snow and Marsh, 1995; Trape and Rogier, 1996). The practical impact of this hypothesis is that: if a child was protected by ITNs but later these were no longer provided or were not used, there might be a rebound effect of clinical disease when the child is exposed to infectious mosquitoes.

Some of carefully controlled efficacy trials that have been running up to 6 years period have shown the benefit of using ITNs in Africa. Results of research project in western Kenya, using randomized controlling trials, showed that ITNs use led to: First, 90% reductions in malaria vector population (Gimnig et al., 2003), 74% reduction in force of infection in infants (ter Kuile et al., 2003a), and 23% reduction in all-cause mortality in infants (excluding neonates) (Phillips-Howard et al., 2003a). Second, no evidence for compromised immunologic antibody response has been confirmed in children less than five years of age (Kariuki et al., 2003). Third, clear beneficial effects on malaria specific morbidity (clinical malaria, malarial anemia) and growth in infants and 1–3 year-old children have been confirmed. Fourth, reduction in exposure to malaria in infancy does not, with continued use of nets for 22 months, result in increased malaria morbidity in one-year-old children (ter Kuile et al., 2003a & b). Fifth, clear reduction in visits of sick children to health facilities associated with ITNs use with concomitant reduction in quantities of antimalarial drugs prescribed (Phillips-Howard et al., 2003b). Sixth, clear benefits associated with pregnancy, including reduced maternal and placental malaria, maternal anemia, and low birth weight (for the first four pregnancies) (ter Kuile et al., 2003b). Seventh, beneficial effects of ITNs spill over into areas adjacent to villages with ITNs; magnitude of this community mass effect is similar to that observed within ITNs villages and dependent upon coverage i.e. the proportion of houses in a given area with ITNs (Hawley et al. 2003; Gimnig et al., 2003). Eighth, evidence for the existence of a community-wide effect due

to marked reduction in vector populations (Howard et al., 2000; Hii et al., 2001; Maxwell et al., 2002), implying that ITNs have substantial effects at the population level. Finally, all these public health benefits of ITNs were sustained for up to 6 years and there is no evidence that bed-net use from birth increases all-cause mortality in older children (Lindblade et al. 2004). All these findings have been demonstrated in areas under setting of intense perennial malaria transmission. More recently, Fegana et al. (2007) associated ITNs use (67% coverage), under different settings of malaria transmission in Kenya, with 44% reduction in mortality in children less than five years.

3. Hazard of pyrethroids insecticides use for ITNs and IRS

Massive use of ITNs began in 1980s following the developmental of photostable synthetic pyrethroids which are faster acting, effective in small quantities, relatively stable adhering to fabric, and relatively safe to human (WHO,1999). Scale up of the ITNs usage has emerged as a key intervention for malaria control in 2000s. The initial aim of Roll Back Malaria (RBM) was to cover 60% of population in malaria endemic countries, which was refined to achieve coverage of 2 bed nets per household. In this case millions of people were expected to be exposed at different dosages of pyrethroids in malaria endemic countries. Washing large quantities of ITNs leading to spill over of insecticide to water bodies could be hazardous to both human and aquatic environment. Likewise regular re-treatment and use of nets as well as use of LLIN's increases the risk of acute toxicity among net dippers and regular users. Also new technology with potential for malaria prevention, such as insecticide impregnated durable wall lining (DL), insecticide treated blankets and tents (e.g. Demuria nets) pre-treated at the factory with high concentration of insecticide, increase the risk of acute toxicity to people doing installation and household occupants coming into contact. In one of WHO's statements regarding the safety of pyrethroid treated mosquito nets (WHO, 1999), it was asserted that if prescribed precautions are followed, field use of these products at concentrations recommended for treatment of mosquito nets poses little or no hazard to people treating the nets or to users of the treated nets. Although other risk assessment of the use of deltamethrin on ITNs largely supports this view of the WHO, a relatively high chronic risk (beyond the US EPA standard of 0.01 mg. active ingredient/kg/body weight) was shown to exist for newborns sleeping under ITNs (Barlow et al., 2001).

All pesticides are toxic by nature and present risks of adverse effects that depend on toxicity of the chemical and the degree of exposure. Toxicity refers to the inherent poisonous potency of a compound under experimental conditions, and chronic toxicity refers to the potential for adverse effects from long-term exposure (Hirsch et al., 2002). While there is agreement that ITNs can be effective in reducing malaria morbidity and mortality under field trials, the adverse effects associated with their use at different level of age groups and sex has not yet to be fully evaluated. Some scientists raised concerns about the long-term effects of ITNs exposures, especially on children and pregnant women (Anyanwu et al., 2004). In their comprehensive literature review, Anyanwu et al. (2006) show that not much work has been done on the effects of long-term exposure to ITNs. But the authors surprisingly concluded that the results of their search on the subject to date seem to support only the efficacy of the temporal use of plain bed nets, but not the use of ITNs, and do not tell much about the long-term effects of ITNs exposure (Anyanwu et al., 2006). Indeed, all pesticides are toxic and have both acute and chronic effects (Ratnasooriya et al., 2003). While there is no doubt about the effectiveness of ITNs and the main challenge now is to scale up

their use (WHO, 2002). Review reports on the benefits of ITNs did not yield any information relating to the potential adverse effects of long-term exposure to insecticide treated products (Anyanwu et al., 2006). However, Kolaczinski and Curtis (2004) concluded that chronic effects can presently not be excluded with certainty, as relevant toxicological data do not exist in the open scientific literature. Properly designed neuro-behavioural studies on groups with long-term exposure to low doses of synthetic pyrethroids should be conducted in order to assess effect of exposure of ITN's. Meanwhile pyrethroids should continue to be used for public health interventions to contribute reducing malaria morbidity and mortality reduction, such as ITNs for malaria control.

On the other hand, IRS insecticides applied indoors of dwellings is subject to a number of considerations and constraints. Similar constraints should apply to new technology under evaluation, such as the durable wall lining (DL) impregnated with high concentration of insecticide, with characteristic of both IRS and LLIN. One of these considerations relates to the required residual effectiveness of the insecticide applied to last the malaria transmission season (Table 4). It is therefore logical that active ingredients (AIs) used in IRS and DL should be biologically available to control the mosquito vectors, but also at the same time potentially available for human uptake via various routes. These routes conceivably include dermal uptake, inhalation (dust and gas phase), and ingestion. As pointed out elsewhere, there probably exists a dynamic redistribution of applied insecticide through a continuous process of indoor sublimation, deposition, and revolatilization, as well as dust movement, necessitating a total home stead environment approach when considering exposure (Sereda et al. 2009). Bouwman and Kylin (2009) showed that infants under malaria control conditions are exposed to combinations of chemicals that would have deleterious effects if the intakes were high enough. They actually showed that the intakes through breast milk do exceed acceptable levels of intake, but they do not attributed the whole level of exposure to insecticides used in malaria control i.e. agricultural and home garden use could also contribute to the levels in the tissue and in breast milk. Generally, the possible resultant toxicity from this exposure could be attributable to either a single compound or combinations of several that could act additively, antagonistically, independently, or possibly synergistically. Critical windows of exposure also need to be considered. The health effects might be transient, reversible, latent, and/or permanent, and might also be subtle and not readily attributable to insecticide use for vector control. Given that IRS and ITNs also effectively reduce morbidity and mortality of malaria, this resulting in a paradox that is a characteristic of many situations where risks and positive outcomes need to be measured and balanced. Because millions of people in malaria control areas experience conditions of multiple sources and routes of exposure to any number of insecticides, even though lives are saved through malaria prevention, identification of potential health risks to infant associated with insecticide residues in breast milk must be incorporated in WHOPES evaluations and in the development of appropriate risk assessment tools (Bouwman and Kylin 2009).

4. Insecticide resistance in insect vectors

Much of the available insecticides for vector control, which have been spectacularly successful in the past, are more than 35 years old (Table 7). For example, early efforts to control malaria during the 1950s and 1960s with spraying indoors with DDT and other insecticides achieved almost total eradication of the vector and the pathogen in many parts of the world (Gramiccia and Beales, 1988; Mabaso et al., 2004; Roberts et al., 2000). These

efforts simultaneously reduced levels of transmission of dengue, leishmaniasis and filariasis. Some countries, such as Taiwan, are now celebrating 40 transmission-free years of malaria. This is a massive achievement, as malaria was previously a major killer in the country (Hemingway et al., 2006). More recently, ITNs reduced morbidity and also mortality from all causes (Phillips-Howard et al., 2003a; Lengeler, 2004). This is a result of protection at the levels of the individual and the community (Lindblade et al., 2004). Control of dengue vectors relies on the removal of larval breeding containers, such as old tyres or flower vases or on insecticide spraying in homes. This approach has been used successfully in some locations, but is not sustainable (Rigau-Perez et al., 2002; Gubler, 1989). Due to insecticide resistance, legitimate environmental and human health concerns, the use of many older generation insecticides, such as DDT is decreasing. The result is that the number of public health insecticides available is dwindling and vector-borne disease transmission is increasing (Hemingway et al., 2006).

Resistance is defined as a heritable change in the sensitivity of a population to an insecticide, which is reflected in the repeated field failure of that product to achieve the expected level of control when used according to the recommendations for that pest species, and where problems of product storage, application and unusual climatic or environmental conditions can be eliminated (McCaffery and Nauen, 2006). Frequent applications of the same insecticide will select for those individuals in a population, with inherent genetic advantage, that are able to survive the recommended dose of the compounds. Over time, this selection pressure will lead to a resistant population becoming established. In such cases, other compounds within the same class of chemistry are in most cases also affected – for instance, resistance to one pyrethroid type usually confers resistance against the whole group of pyrethroids, a phenomenon known as cross-resistance. Sometimes, depending on the nature of the resistance mechanism, cross-resistance can occur between different chemical classes, for example organophosphates and carbamates, and cross resistance between DDT and pyrethroids (multi-resistance). Furthermore, resistance development due to selection pressure in disease vectors is sometimes complicated by an additional (perhaps sometimes neglected) aspect: the frequent application of similar synthetic insecticides to control pests of agricultural importance. This may indirectly affect the susceptibility of insects of public health importance, because that is where the vectors are additionally exposed to pesticides used for agricultural purpose (Brogdon and McAllister, 1998; Liu et al., 2006; Hemingway and Ranson, 2000; Nauen, 2007).

4.1 Insecticide resistance mechanisms

Four classes of chemical insecticides are the mainstay of vector control programmes: namely organochlorines, organophosphates, carbamates, and pyrethroids (WHO, 2006a). To date, four types of resistance mechanisms against the chemical insecticides have been described: metabolic resistance, target site resistance, penetration resistance, and behavioural resistance. Metabolic and target site resistance have been extensively investigated at both the genetic and molecular levels (Hemingway and Ranson, 2000). Metabolic resistance involves the sequestration, metabolism, and/or detoxification of the insecticide, largely through the overproduction of specific enzymes (Hemingway and Karunaratne, 1998; Hemingway et al., 1998). So far, three main groups of enzymes have been identified in different insect vectors species (Table 7): carboxylesterases (EST: efficient against organophosphate and carbamate insecticides), glutathione- S-transferases (GST: efficient against organophosphates, organochlorine, and pyrethroid insecticides) and cytochrome P450-dependent monoxygenases (MOX: efficient against most insecticide types, frequently

Years	WHO approved insecticides			Comments
1940-45	DDT			
1946-50	Lindane			
1951-55	Malathion			Only a limited number of insecticide classes are available for insect vectors control. No new insect vector adulticide has been approved by the WHO the last 20 years.
1956-60				
1961-65	Fenitrothion	Propoxure		
1966-70	Chlorpyrifose-methyl			
1971-75	Pirimiphose-methyl	Bendiocarb	Permethrin	
1976-80	Cypermethrin			
1981-85	Alpha-cypermethrin	Cyfluthrin		
	Lambada-cyhalothrin	Deltamethrin	Bifenthrin	
1986-90	Etofenprox			
1991-95				
1996-00				
2001-05				
2006-10				
	Organochlorines		Carbamates	
	Organophosphates		Pyrethroids	

[1]Adapted from Nauen, 2007.

Table 7. History of WHO-approved insecticides for adult malaria mosquito control.[1]

in conjunction with other enzymes). The overproduction of these enzymes may be achieved via two nonexclusive mechanisms: gene amplification increasing the gene's copy number (Hemingway et al., 1998) and gene expression via modifications in the promoter region or mutations in trans-acting regulatory genes (Hemingway et al., 1998; Rooker et al., 1996). In addition, in some mosquito species, carboxylesterase resistance to the insecticide malathion has been associated with a qualitative change in the enzyme (a few amino acid substitutions can increase the rate of hydrolysis of the enzyme (Hemingway et al., 2004). In contrast, target site resistance is achieved by point mutations that render the actual targets of an insecticide less sensitive to the active ingredient (Hemingway and Ranson, 2000; Weill et al., 2003). Most insecticides developed to date are neurotoxic and aim for one of the following three targets: the acetylcholinesterase (AChE) (whose role is the hydrolysis of the neurotransmitter acetylcholine), the c-aminobutyric acid (GABA) receptors (chloride-ion neurotransmission channels in the insect's nervous system), or the sodium channels (responsible for raising the action potential in the neurons during the nerve impulses). The acetylcholinesterase is the target of organophosphorous and carbamate insecticides, the GABA receptors are the main targets of cyclodiene (organochlorine) insecticides, and the sodium channels (resistance by modification of this site known as knockdown resistance

(KDR)) are the targets of pyrethroid and organochlorine insecticides. Mutations in all these three sites can confer resistance (Table 8).
More recently, two alternative insecticide types have been introduced, largely for the control of mosquito larvae: bio-pesticides (e.g., Bacillus thuringiensis, Bacillus sphaericus) and insect growth regulators, such as the juvenile hormone mimic and methoprene (WHO, 2006a). Cases of resistance to these alternative insecticides are still limited (Rivero et al., 2010) and the underlying mechanisms are only beginning to be identified (Chalegre et al., 2009; Darboux et al., 2007).

Vector	Pathogen (Disease)	Insecticide Resistance	
		Metabolic	Target Site
Diptera (mosquitoes, flies)			
Aedes sp.	Brugia, Wuchereria (lymphatic filariasis), yellow fever virus, dengue virus, encephalitis virus	EST	KDR
		GST	GABA
Anopheles sp.	Plasmodium sp. (malaria), Wuchereria (filariasis)	EST	KDR
		GST	AChE
		MOX	GABA
Culex sp.	Wuchereria (filariasis), West Nile virus, encephalitis virus	EST	KDR
		GST	AChE
		MOX	GABA
Phlebotomus sp.	Leishmania sp. (leishmaniasis)	EST	AChE
Simulium sp.	Onchocerca sp. (river blindness)	EST	-
Haemiptera (true bugs)			
Rhodnius sp.	Trypanosoma sp. (Chagas disease)	?	?
Triatoma sp.	Trypanosoma sp. (Chagas disease)	EST	-
		MOX	
Phiraptera (body lice)			
Pediculus sp.	Rickettsia sp. (epidemic thyphus)	?	?
Siphonaptera (fleas)			
Xenopsylla sp.	Pasturella (bubonic plague)	?	?

[1]Adapted from Rivero et al. (2010).
Metabolic resistance: EST, enhanced esterase activity; GST, enhanced glutatione-S-transferase activity; MOX, enhanced p450 monoxygenase activity. Target site resistance: AChE, modification of the acetylcholinesterase; GAB, modification of the GABA receptors; KDR, (knockdown resistance) modification of the sodium channels. ?, Insecticide resistance present but mechanism unknown or unconfirmed to the best of our knowledge.

Table 8. Insecticide resistance mechanisms reported to date in natural populations of the main insect vectors of human diseases[1].

4.2 Resistance and disease control

To compromise insecticide vector control, the level of resistance must be high enough to adversely affect disease transmission. In many cases, vector control may not be affected by the level of resistance. For example, an activity may be controlling only 75% of the vector population. If, for example, the level of resistance is lower than 10%, resistance will

not affect disease control efforts; in this situation, increasing surveillance and monitoring level and frequency of resistance would be sufficient. No change in control methods would be needed (Brogdon and McAllister, 1998). Western Kenya is a good operational example of the coexistence of resistance and disease control. Pyrethroid resistance appeared soon after bed nets were introduced in Kenya. After 2 years, the resistance level had not changed significantly, possibly because of the continual introduction of susceptible genes (Vulule et al., 1996). Other reasons may explain why the presence of insecticide resistance genes in vectors in a control area does not mean that effective control is not being achieved. For example, resistance genes may not be expressed, they may be expressed in an alternative stage of development to that being controlled by insecticide, or the gene detected may be a member of an alternative gene subfamily to one that can affect the compound being used (Brogdon and McAllister, 1998). For example, in *An. albimanus,* resistance enzymes, especially esterases and GST, may be expressed only in freshly emerged adult anophelines and may be absent in older mosquitoes, those potentially infectious for malaria (Brogdon et al., 1999). In six populations of *An. arabiensis* from Sudan, the L1014F-kdr resistance allele present in 66% dead individuals against the WHO discriminating concentrations of permethrin (Himeidan et al., 2011) suggesting that another factor in the para-type sodium channel gene might be needed for the expression of kdr resistance phenotype (Brooke, 2008).

Insecticide resistance is viewed as an extremely serious threat to crop protection and vector control, and is considered by many parties, including industry, the WHO, regulatory bodies and the public, to be an issue that needs a proactive approach. In 1984, the Insecticide Resistance Action Committee (IRAC) was formed in order to provide a coordinated private-sector response to prevent or at least delay the development of resistance (www.irac-online.org) (McCaffery and Nauen, 2006).

The Innovative Vector Control Consortium (IVCC) was formed in 2005, with an initial grant of $50.7 million from Bill & Melinda Gates Foundation over five years, as a new initiative to enable industry and academia to join forces to improve the portfolio of chemical and technological tools available to reduce vector-borne diseases. Since then, an unprecedented development pipeline of new, reformulated and repurposed insecticides has been established in partnership projects with leading global chemical companies. A suite of information systems and diagnostic tools for the more effective and efficient use of insecticides has also been developed, with these products now nearing the end of their development phase and being readied for rollout in the coming year. Accordingly, IVCC has received another $50 million in 2010 from the Bill & Melinda Gates Foundation to continue its work to develop new insecticides for the improved control of mosquitoes and other insects which transmit malaria, dengue and other neglected tropical diseases. As resistance to insecticides is increasing at an alarming rate and it must find new alternatives insecticides against malaria vectors and other vector borne diseases, the strategic aim of IVCC is to provide three new Active Ingredients for use in public health insecticides by 2020.

5. Authors' contributions

YEH identified the idea, drafted and wrote up the chapter, EJK and EAT critically reviewed the content and proof read the chapter. All authors read and approved the final chapter.

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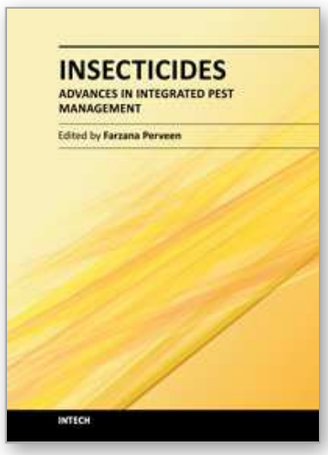

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This book contains 30 Chapters divided into 5 Sections. Section A covers integrated pest management, alternative insect control strategies, ecological impact of insecticides as well as pesticides and drugs of forensic interest. Section B is dedicated to chemical control and health risks, applications for insecticides, metabolism of pesticides by human cytochrome p450, etc. Section C provides biochemical analyses of action of chlorfluazuron, pest control effects on seed yield, chemical ecology, quality control, development of ideal insecticide, insecticide resistance, etc. Section D reviews current analytical methods, electroanalysis of insecticides, insecticide activity and secondary metabolites. Section E provides data contributing to better understanding of biological control through Bacillus sphaericus and B. thuringiensis, entomopathogenic nematodes insecticides, vector-borne disease, etc. The subject matter in this book should attract the reader's concern to support rational decisions regarding the use of pesticides.

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