Chapter 22

Vector Control: Some New Paradigms and Approaches

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Context

The World Malaria Report 2012 [1] summarizes data received from 104 malaria-endemic countries and territories for 2011. Ninety-nine of these countries had on-going malaria transmission. According to the latest World Health Organization (WHO) estimates, there were about 219 million cases of malaria in 2010 and an estimated 660,000 deaths. Africa is the most affected continent: about 90% of all malaria deaths occur there.

Malaria surveillance systems detect now only around 10% of the estimated global number of cases. In 41 countries around the world, it is not possible to make a reliable assessment of malaria trends due to incompleteness or inconsistency of reporting over time.

Actually another estimation of mortality [2] gave the following figures of 1,238,000 (929,000-1,685,000) deaths in 2010. This "one to two" ratio for the same year is matter of concern when considering that the main target of RBM is to reduce by 50% the burden of malaria.

The Lives Saved Tool (LiST) was developed to provide national and regional estimates of cause-specific mortality based on the extent of intervention coverage scale-up in sub-Saharan Africa and it appeared that it "performed reasonably well at estimating the effect of vector control scale-up on child mortality when compared against measured data from studies across a range of malaria transmission settings and is a useful tool in estimating the potential mortality reduction achieved from scaling-up malaria control interventions" [3].

Three major issues deserve special attention: tools for vector control, resistance of mosquito to insecticides, of *Plasmodium* to drugs, of human population to change their behavior, and costs. To tackle these issues new paradigms must be developed with the objectives of efficacy, acceptability and cost-efficiency.

Vector control remains the most generally effective measure to prevent malaria parasite transmission and therefore was one of the four basic technical elements of the Global Malaria Control Strategy [4]. Through the 1980s', vector control was mainly based upon Indoor Residual Spraying (IRS) and, in some circumstances, larval control, but an important break-through occurred with Insecticide Treated Nets (ITNs) then Long Lasting Insecticide treated Nets (LNs) (Figure 1) were introduced. The large scale implementation of ITN has, in several epidemiological settings, produced striking reductions in malaria transmission (-90%), incidence rate of malaria morbidity (-50%) and overall infant mortality (-17%) [5].

For WHO to achieve universal access to long-lasting insecticidal nets (LLINs), 780 million people at risk would need to have access to LLINs in sub-Saharan Africa, and approximately 150 million bed nets would need to be delivered each year. The number of LLINs delivered to endemic countries in sub-Saharan Africa dropped from a peak of 145 million in 2010 to an estimated 66 million in 2012 [1]. This will not be enough to fully replace the LLINs delivered 3 years earlier, indicating that total bed net coverage will decrease unless there is a massive scale-up in 2013. A decrease in LLIN coverage is likely to lead to major resurgences in the disease. In 2011, 153 million people were protected by indoor residual spraying (IRS) around the world, or 5% of the total global population at risk. In the WHO African Region, 77 million people, or 11% of the population at risk were protected through IRS in 2011.

Recent field observations have shown that LLINs may not be as durable as previously estimated and the majority of the most commonly distributed LLINs may have a shorter effective material life, which induce a higher than scheduled cost of global malaria control when LLIN have to be changed more frequently than expected. The problem of cost is a burning issue. International disbursements for malaria control rose steeply during the past eight years and were estimated to be US$ 1.66 billion in 2011 and US$ 1.84 billion in 2012. National government funding for malaria programmes has also been increasing in recent years, and stood at an estimated US$ 625 million in 2011. However, the currently available funding for malaria prevention and control is far below the resources required to reach global malaria targets. An estimated US$ 5.1 billion is needed every year between 2011 and 2020 to achieve universal access to malaria interventions. In 2011, only US$ 2.3 billion was available, less than half of what is needed ([1] fact sheet).

In its 23rd meeting in Senegal, the RBM Partnership Board concluded with an urgent call to governments of malaria endemic countries and development partners to secure the US$2.4 billion needed over the next two years to maintain high levels of coverage with life-saving malaria prevention and treatment interventions in eight African countries. This call follows a decade of success where *malaria deaths have fallen by over one-third in sub-Saharan Africa*.

Overall, out of a total of US$6.8 billion required, US$3.2 billion has been mobilized leaving a US$3.6 billion gap to make sure all affected countries in Africa have enough insecticide treated nets, effective treatments and rapid diagnostic tests for all populations at risk of malaria to achieve the target of near-zero deaths by 2015.

In term of vector control several issues deserve special attention. The change in vector behavior from indoor to outdoor feeding under insecticide pressure may limit the impact of classical

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control interventions such as LNs and IRS which target indoor feeding and resting mosquitoes and new tools are obviously needed. On the other hand, species that naturally bite and spend most of their time outdoors such as *Anopheles dirus* in S.E. Asia are poorly controlled by these classical tools and new approaches are urgently needed.

Vector control is also threatened by *the development of insecticide resistance* [4-9]. The frequency of resistance, has risen sharply over the last decade and the relationship between current indicators of resistance and the impact of vector control interventions is still unclear according to the different mechanisms of resistance, though most scientists believe that at some point in the near future resistance will begin to compromise control efforts, and new active ingredients to replace the current ones are urgently needed. Mosquito resistance to at least one insecticide used for malaria control has been identified in 64 countries around the world. In May 2012, WHO and the Roll Back Malaria Partnership released the Global Plan for Insecticide Resistance Management in malaria vectors, a five-pillar strategy for managing the threat of insecticide resistance.

Overcoming insecticide resistance will require novel chemical modes of action or combined interventions, with multiple active agreements, used as part of an integrated vector management strategy or completely new tools to delay the emergence of resistance by reducing selection pressure (e.g. rotations), or kill resistant vectors by exposing them to multiple insecticides (e.g. mixtures, when they become available).

Thus, new paradigms and approaches to vector control will expand the range of species that can be controlled and the chemical modes of action that can be employed, as well as potentially reducing the costs and complications of delivering them.

1.2. Definitions (from Innovative Vector Control Consortium IVCC)

A paradigm can be defined as a mean to deliver an active ingredient to the vector by targeting certain behaviors or ecologies. Paradigms can be associated with general chemical modes of action. Tools that target mosquito resting employ contact toxins. Those based on sugar feeding employ the so-called stomach poisons, etc. New paradigms open the door for exploitation of new chemical modes of action. An intervention paradigm (current examples: Insecticidal Nets or Indoor Residual Spray) is characterized by a primary mode of action (e.g. kills insect that land on the walls) and key characteristics such as the way it applied, its distribution process, economics, user, acceptability etc.

A paradigm may be served by several categories of products, each of which is described by a Target Product Profile (TPP) (e.g. ITNs *vs*. LLINs). The TPP will describe the primary functionality and characteristics that are required of a product to achieve a particular epidemiological outcome. Individual products within the category are defined by specifications.

Figure 1 illustrates the relationship among behaviors, paradigms and chemical mode of action. Where new paradigms do not exist in public health an example from agriculture or home and garden products is listed instead.

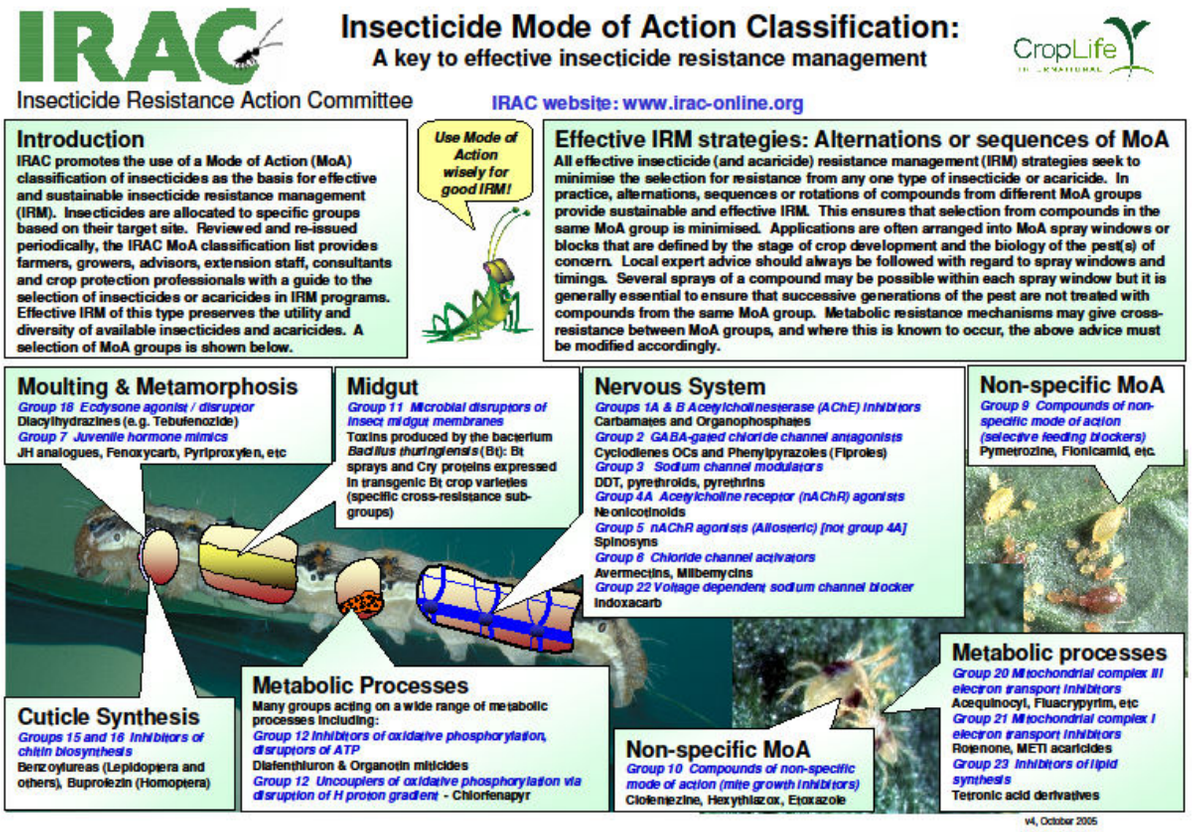

Figure 1. Relationship among behaviors, paradigms and chemical mode of action of insecticides.

2. New approaches to existing paradigms

2.1. New long lasting insecticide formulation for IRS

A microencapsulated formulation (CS) of the organophosphate chlorpyrifos methyl has recently been developed as long lasting i.e., alternative to DDT. In experimental huts in South Benin, against pyrethroid resistant (*kdr* + metabolic resistance) *An. gambiae* M form (and *Cx. quinquefasciatus*), chlorpyrifos methyl (Figure 2) was used to treat mosquito nets, and for IRS, and was compared to other commonly used insecticides: DDT and lambdacyhalothrin [10].

On nets, for N'Guessan et al [10] "the percentage of mortality among *An. gambiae* was 45.2% with the chlorpyrifos methyl-treated net and only 29.8% with the lambacyhalothrin-treated net. Mortality rates among *Cx. quinquefasciatus* were lower than among *An. gambiae* and did not exceed 15% with either type of treated net". While "Mortality of pyrethroid resistant *An. gambiae* was 95.5% with chlorpyrifos methyl-IRS compared to 50.4% in the hut sprayed with DDT and 30.8% in the hut sprayed with lambdacyhalothrin. The mortality of *Cx. quinquefas-*

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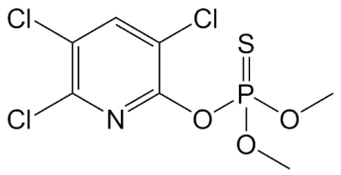

Figure 2. Chemical formula of chlorpyrifos methyl

ciatus in the chlorpyrifos methyl-IRS huts was 66.1% whereas in the DDT and lambdacyhalothrin-IRS huts it was only 14%". Therefore "chlorpyrifos methyl-IRS showed greater potential than DDT of lambdacyhalothrin-IRS for control of pyrethroid resistant *An. gambiae* M form and *Cx. quinquefasciatus* in areas of high *kdr* frequency" [11].

In terms of mortality the short residual activity of chlorpyrifos methyl on ITN is of great concern with a mortality rate decreasing from 100% to 9.7% within just one month while as IRS on cement it was observed "no loss of activity during the nine months of follow-up" compared to the fast decay of DDT and lambdacyhalothrin observed within the first month of spraying. A 9-month efficacy could be very valuable in many West and East African endemic countries with malaria transmission seasons lasting less than 8 months, and where IRS application of chlorpyrifos methyl each year could be adequate. In areas with developing pyrethroid resistance one might envisaged continued use of pyrethroid LLIN in combination with IRS, rotating the use of chlorfenapyr and CS long lasting chlorpyrifos methyl formulation.

2.2. New insecticides paints combining several insecticides and an insect growing regulator for IRS

Insecticide paints are new interesting paradigm for vector control with several advantages regarding classical IRS. It may provide future possibilities to combine several active ingredients in one product and therefore be used to help manage insecticide resistance. Paints can be produced in different colors to fit with people's choice. They may also be potentially implementable by households without the need for a specialized team to deliver the intervention, as is the case with IRS. This could improve community and household acceptance and uptake. Paints may also have the potential of being longer lasting than IRS. Insect growth regulator (IGR), a product usually used as larvicides, is also now being evaluated in Inesfly® 5A IGR™, a paint designed to target adult mosquitoes. Inesfly® 5A IGR™ is composed of two organophosphates (OPs), chlorpyriphos (1.5%), and diazinon (1.5%) and pyriproxyfen (0.063%) an IGR which was successfully used against *Triatoma infestans* [12]. The product is white vinyl paint with an aqueous base. Active ingredients reside within Ca CO3 + resin microcapsules. The formulation allows a gradual release of active ingredients, increasing its persistence.

In Benin the Inesfly® insecticide paint has been tested in laboratory [13] and in field [14] studies. In the laboratory study, the paint was tested against laboratory strains of the urban pest *Cx. quinquefasciatus* the susceptible (S-Lab) strain and the SR homozygote for the ace-1R resistant gene involved in the resistance to OPs and carbamates, with classical bioassay cones (tests on 30 min). Efficacy was measured not only in terms of induced mortality but also in terms of fecundity (number of eggs laid), fertility (% hatching) and larval development (%

pupation and % emergence). Insecticidal paints were tested at different time points: T0, 6 (= 6 months), 9 (= 9 months) and 12 months after application on four different surfaces: softwood, hard plastic (non-porous materials), ready-mixed cement and ready-mixed stucco (porous materials) at two doses, 1kg/6 m^2 (manufacturer's recommended dose to obtain surfaces completely white) and 1 kg/12 m^2. Female mosquitoes were given a blood meal 36 hours after standardized exposure to the painted surfaces. The study showed that the highest rates of mortality were obtained by both doses on susceptible as well as resistant strains even 12 months after treatment, on non-porous surfaces (softwood, plastic), whereas, on porous surfaces (cement, stucco) efficacy was much lower on resistant than on susceptible strain and it dropped to almost 0 at 6 and 12 months in both strains.

Thus long-term efficacy was an issue of porosity of materials rather than the pH of materials or the dose applied. It should be noted that 100% mortality was achieved on non-porous surface even against the OP resistant strain.

In terms of fecundity, fertility, and larval development, "a significant reduction in the number of eggs laid was shown at 0 and 9 months after treatment at either dose. A reduction in egg hatching was observed at T0, but not at T9. An increased mortality from the nymph to the adult stage was shown 9 months after treatment at the higher dose. No differences were found on the duration of the larval development. No IGR effect was observed 12 months after treatment". The percentage of emergence (i.e. adult emerging from pupa) dropped from 80% in control to #53% in samples from exposed females. Hence an adulticide could have impact not only on longevity of females exposed but also on their offspring which is a great advantage for mosquito population control.

Field trials were conducted in area where the local population of *An. gambiae* is composed of the M molecular form with resistance to pyrethroids and DDT, *kdr* is present at a high frequency, but is susceptible to OPs and carbamates, the ace-1R mutation was absent. *Cx. quinquefasciatus* shows high resistance to DDT, pyrethroids and carbosulfan with high *kdr* frequency and elevated levels of esterases and GST activity but the ace-1R mutation was absent [9]. In these trials, experimental huts were treated with either 1 or 2 layers of insecticide paint at one dose (6 kg/m^2). Treatments were applied to either just walls, or to walls plus the ceiling. Unfed females of the lab-reared *An. gambiae* Kisumu strain (sensitive to all insecticides), were tested against local resistant wild strain *An. gambiae* and *Cx. quinquefasciatus*. The *An. gambiae* Kisumu strain mosquitoes were placed inside the huts at a distance of 1 m from two perpendicular walls, and left from 19:00 to 7:00 h [14]. The wild strains were tested using the standard WHO bioassay method.

Mortality of wild resistant *An. gambiae* was high with 83% even 9 months after treatment (2 paint layers on walls). Mortality of wild resistant *Cx. quinquefasciatus* was >50% even 9 months after treatment (2 paint layers on walls). No deterrent or excito-repellent effect was observed against *An. gambiae* nor *Cx. quinquefasciatus*. Mortality rates of exposed *An. gambiae* Kisumu strain in distance experiments in huts (1 m from two perpendicular walls; see above) with 2 layers were most striking, because even one year after treatment 100% of these sensitive mosquitoes were killed (Figure 3C).

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Classical cone bioassay showed that in huts with 2 layers "twelve months after treatment mortality rates were of 70-80% against *An. gambiae* and *Cx. quinquefasciatus*". Release of insecticide susceptible unfed *An. gambiae* specimens in huts treated but without net (untreated) showed that 2-13% of females took their blood meal while 72% were well blood fed in control huts. Mortality rates observed in distance experiments were most striking, (Figures 3A & 3B) and even one year after treatment 100% of exposed *An. gambiae* Kisumu strain specimens were killed in huts with 2 layers (Figure 3C).

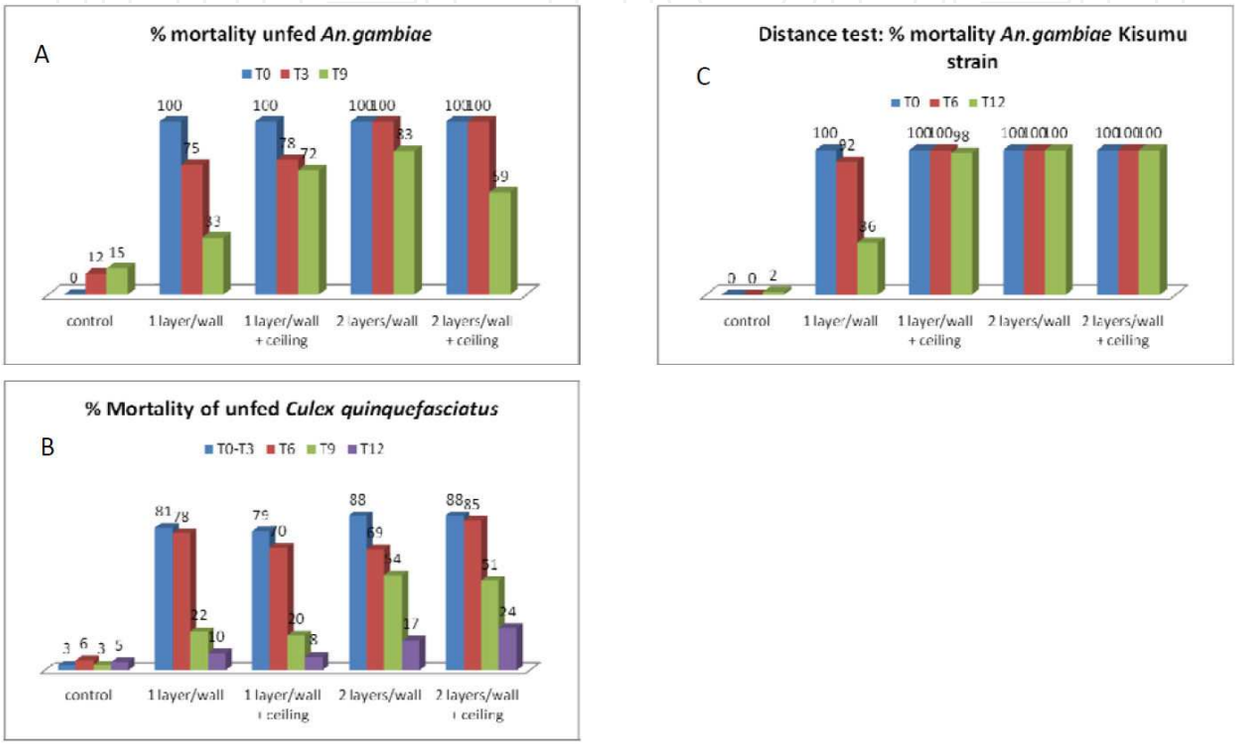

Figure 3. Mortality rates observed in distance experiments of exposed unfed *Anopheles gambiae* (A), unfed *Culex quinquefasciatus* (B), and *Anopheles gambiae* Kisumu strain (C) observed after 3 or 6 or 9 or 12 months after treatment (T3, T6, T9, T12 respectively).

These observations of "volume effect", "layer effect", "substrate effect", residual efficacy duration, and its efficacy against susceptible and resistant strains of the malaria vector *An. gambiae* and the nuisance insect *Culex quinquefasciatus*, are very encouraging. The paints ability to reduce mosquito fecundity and egg hatching opens up interesting new perspectives on malaria and mosquito control for urban settings where walls are commonly constructed with brick, concrete and plaster and provide suitable surfaces for paints, unlike classical mud made wall houses that characterize most rural communities. The paints ability to also reduce *Culex* mosquitoes is likely to increase community acceptance and maintenance of paint.

2.3. New mode of action families for IRS usage: Neonicotinoids

Neonicotinoid insecticides act on the central nervous system of insects by binding of agonist on postsynaptic nicotinic receptors [15]. Discovered in 1998, dinotefuran is a novel neonicoti-

noid insecticide which belongs to the third-generation neonicotinoids (sub-class: furanicotinyl compounds) [16]. It is a neonicotinoid agonist of the nicotinoid acetylcholine receptor with no cross-resistance to other insecticides such as organochlorine (OC), organophosphate (OP), carbamates or pyrethroids. Its efficiency is not greatly diminished by the presence of resistance mechanisms such as *kdr* or ace-1^R in mosquitoes.

In studies comparing the impact of dinotefuran, permethrin and propoxur on resistant strains of *Cx. quinquefasciatus*, dinotefuran was about 10 times more effective than permethrin on the BKPER strain, and 1000 times more effective than propoxur on resistant R-LAB strain [17]. If this product can be incorporated into material (e.g. LNs) or IRS applications then it should be useful in areas where resistance to pyrethroids and carbamates has developed.

The option of associating insecticides with different modes of action is one of the possible strategies for resistance management (as developed in another Chapter by Corbel & N'Guessan). An interesting approach that has recently been studied, combined Piperonyl butoxide (PBO), organic compound used as pesticide synergist, and dinotefuran in an attempt to restore the efficacy of deltamethrin treated mosquito net against resistant *An. gambiae* [18]. Darriet and Chandre [18] have also conducted classical laboratory cone tests of nets treated with deltamethrin, PBO (the classical synergist, inhibitor of oxidases) and dinotefuran alone or in combination against susceptible ("KIS") and resistant '("VKPR") strains of laboratory reared *An. gambiae*. Results of these tests are summarized in Table 1.

Product/ strain		**KIS**			**VKPR**	
	mortality	KDt50	KDt95	mortality	KDT50	KDT95
Deltamethrin	100%	8′	18′	7.5%	31′	194′
Dinotefuran				39%	No	No
PBO				4%	No	No
Deltamethrin +PBO				58%	13′	36′
Dinotefuran + PBO				28%	No	No
Deltamethrin+ Dinotefuran + PBO				99%	10′	23′

Table 1. Effects of mosquito nets treated with deltamethrin, PBO and dinotefuran on susceptible ("KIS"), and resistant '("VKPR") strains of *Anopheles gambiae.*

WHO's minimum mortality level for insecticides is 80% and this provides a reasonable operational guideline for effectiveness. In this study PBO combined with deltamethrin increased significantly its efficacy (synergistic effect), but not to a level adequate for control against pyrethroid-resistant mosquitoes, "suggesting that the acetylcholine concentration within the synaptic gap probably also increased". Interestingly, PBO had an antagonistic effect when combined with dinotefuran, decreasing this insecticide's efficacy. However, when PBO

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and Dinotefuran were combined with deltamethrin, the combination resulted in 99% mortality against the pyrethroid resistant mosquito strain, comparable with deltamethrin treated nets (in terms of mortality and KD effect) on the fully susceptible mosquito strain. For Darriet and Chandre [18] "the concomitant action of enhanced acetylcholine concentration in the synaptic gap and inactivation of nicotinic receptors by dinotefuran probably explains the strong synergy observed after exposure to the three-compound mixture, which caused nearly 100% mortality in a pyrethroid-resistant strain of *An. gambiae*".

2.4. New Insecticide Treated Plastic Sheeting (ITPS) and Durable Wall Linings (DL or WL)

Insecticide Treated Plastic Sheeting (ITPS) was developed in 2001 to provide a dual purpose tool capable of providing effective shelter and malaria control to displaced families in humanitarian crises. Durable wall linings (DL), developed in 2005, follow similar principles to ITPS, but are designed to be applied to the surface of existing rural house walls. In both cases these tools were developed to overcome the operational complexities and short comings of IRS, increase user acceptance (as the materials are available in different colors), and to increase residual insecticide activity (from classical 3-6 months with IRS to multiple years with ITPS or DL), and to increase community participation with a tool that households can implement themselves, and finally to provide new tools and new insecticide delivery mechanisms within the framework of insecticide resistance management. To date all factories produced ITPS based on solid format of polyethylene treated with pyrethroid insecticide, either permethrin or deltamethrin. The first generation of DL is also a polyethylene, but in 50% shading material format (woven polyethylene threads, with equal sized spaces between the threads).

One study group [19] has used "plastic sheeting impregnated with carbamates combined with long-lasting insecticidal mosquito nets for the control of pyrethroid-resistant malaria vectors" but this version of ITPS is unlikely to be tested at Phase III level or commercialized due to significant toxicity and fire risk problems associated with carbamates in this format. Different commercial products have been developed with different deltamethrin surface concentrations such as "ZeroVector (DL)" (170 mg a.i./m^2) or "Zero Fly" (360 mg a.i./m^2). Zerofly ITPS have been studied (Phase II) in refugee's camps in Afghanistan [20], in Sierra Leone (Phase III) [21], as well as in India (in endemic area with *An. culicifacies* and *An. fluviatilis* vectors or laborer settlements with *An. culicifacies* and *An. stephensi* as vectors) [22-23].

In Angola, a Phase III field trial was implemented in rural area, 8 villages around Balombo which were paired and received LLIN PermaNet 2.0 (55 mg a.i./m^2; Figures 3) or DL/WL ZeroVector or LLIN + ITPS "Zero Fly" or IRS with lambdacyhalothrin (25 mg a.i./m^2) with comprehensive evaluation: entomology, parasitology and immunology; focus group and KAP surveys were also implemented to follow the household acceptability of the vector control methods introduced.

The main vector in these villages was *An. funestus*. Entomological and parasitological first studies results showed that deltamethrin treated DL ZeroVector alone gave same results as IRS (lambdacyhalothrin) or LLIN (PermaNet®) alone or both PermaNet + ITPS Zero Fly in reducing by 55% the *P. falciparum* prevalence and parasitic load in children 2-9 years old (Figure 5) [24].

Figure 4. LLIN PermaNet 2.0 inside a house in Caala village (A); Green DL/WL ZeroVector inside a house in Chisséquélé village (B); Silver DL/WL ZeroVector inside a house in Barragem village (C); LLIN PermaNet 2.0 + ITPS Zero Fly in a house of Capango village (D) (Photos by P. Carnevale).

Entomological data obtained by classical CDC light traps inside houses before/after implementation of vector control measures were in line with the clinical results i.e. similar level of reduction of number of *Anopheles* in each village (Figure 6) such as 79.1% reduction all villages combined [24].

Immunological analysis of antibodies directed against saliva proteins of *Anopheles* [23] (Figure 7) confirmed the actual reduction of man/*Anopheles* contact with ITPS as well as IRS while association LLIN + ZF gave the best result.

A series of smaller Phase II DL/WL feasibility and acceptability studies, with entomological monitoring have also been conducted in Angola and Nigeria [25], Equatorial Guinea, Ghana, Mali, South Africa and Vietnam [26], and Papua New Guinea [27]. In each of these Phase II village studies, DL/WL acceptability data were collected using a standardized household survey used by each of the different study groups, with the conclusive result that DL/WL had an extremely high acceptance level amongst all cultures and communities in which it was

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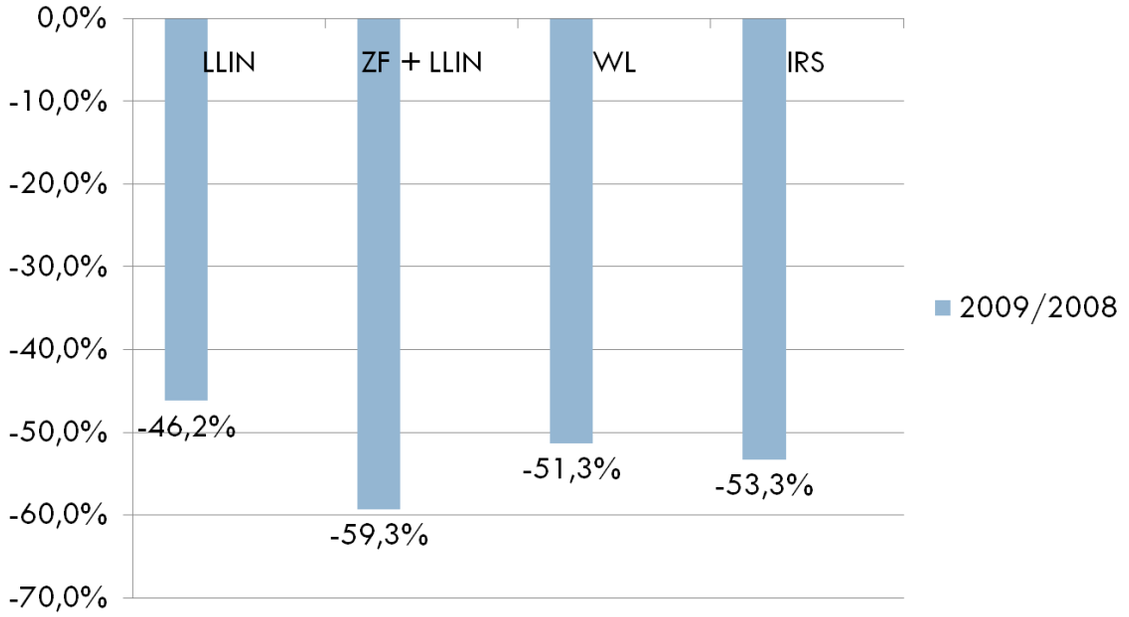

Figure 5. Regressive evolution of endemicity indice (plasmodic indices of 2 – 9 years old children) before/after implementation of each one of the four vector control methods.

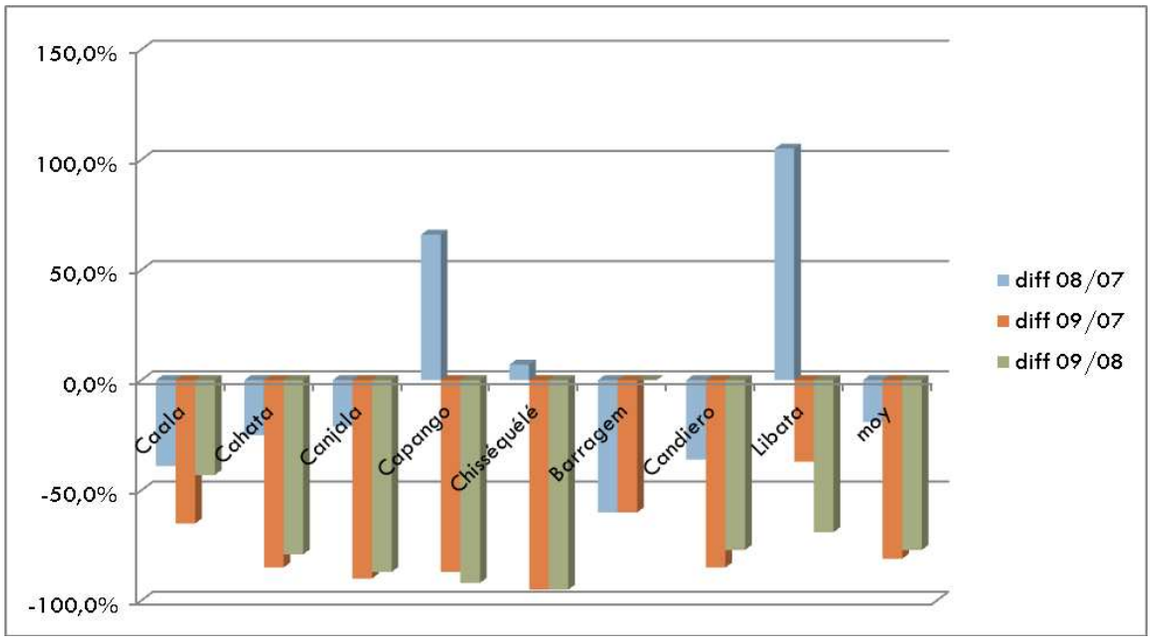

Figure 6. Reduction of number of *Anopheles* in CDC light trap sampling inside houses in villages before (2007-2008) and after (2009) vector control implementation [Caala and Cahata = LLIN alone; Canjala and Capango = LLIN + ZF; Barragem and Chisséquélé = WL alone; Candiero and Libata = IRS.

tested, and that when compared to IRS it was the preferred malaria prevention tool in every study. DL/WL proved feasible in every country study and in all house construction types tested, including brick, mud, wooden, and concrete walled rural houses. In each of these

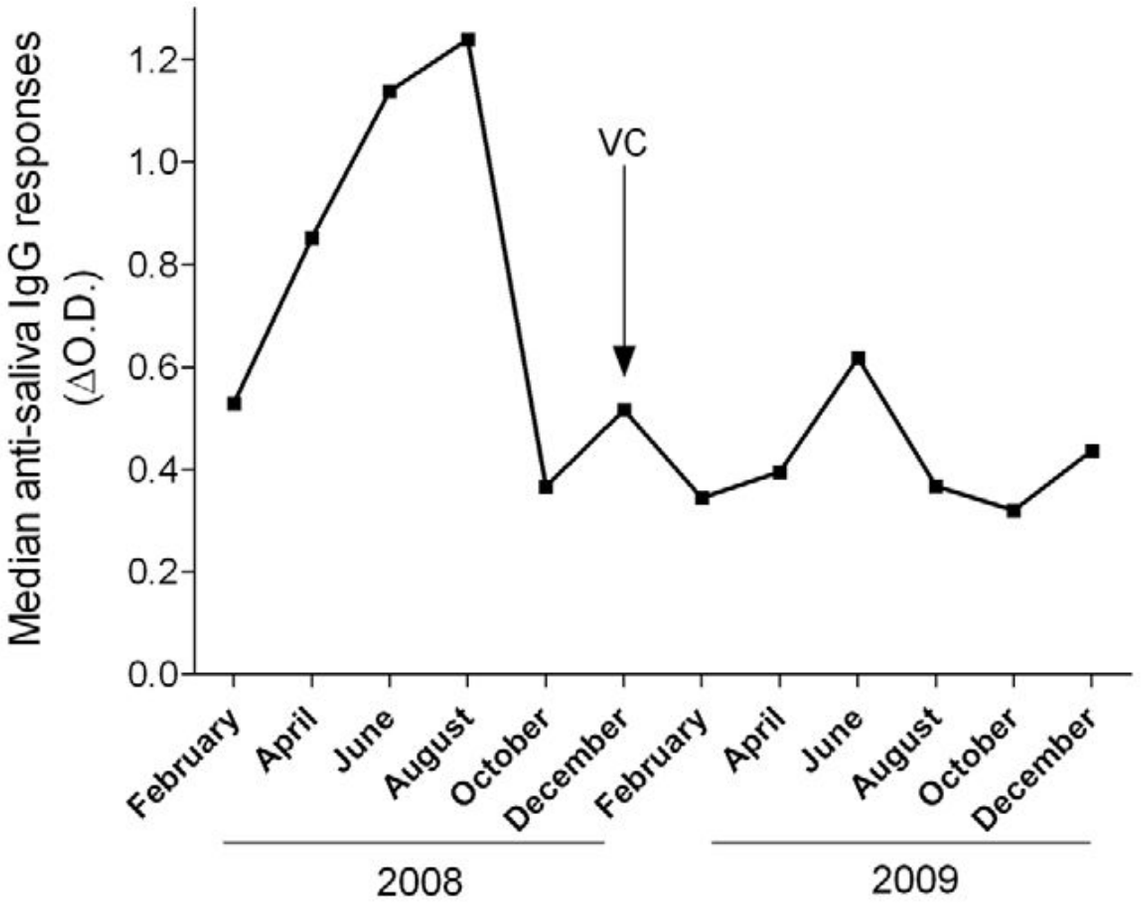

Figure 7. Evolution of the median values of the IgG antibody response to *Anopheles* saliva for all 6 villages combined according to the survey period in 2008 and 2009 (VC: vector control methods implemented in December 2008) [24].

studies, samples of DL/WL were collected at 4 monthly time intervals and were examined for deltamethrin residual content and bioassay impact on vector mosquitoes. The different studies produced very similar results regardless of house construction type, and in all cases DL/WL retained full activity and achieved >90% mortality of vector mosquitoes for the full monitoring periods of each study. The minimum study monitoring period was 6 months and the maximum was 4 years.

In Sierra Leone, Burns et al [21] conducted a Phase III study of ITPS. They constructed two refugee camps, Largo and Tobanda, using ITPS in 50% of each camp for shelter construction. The remaining 50% of each camp had shelter constructed out of untreated plastic sheeting (UPS). In Largo Camp, ITPS/UPS was applied onto walls and the ceiling of each shelter. In Tobanda Camp, ITPS/UPS was used only on ceilings. In Largo, the *Plasmodium falciparum* incidence rate in children up to 3 years of age who were cleared of parasites and then monitored for 8 months, was 163/100 person-years under UPS and 63 under ITPS. In Tobanda, incidence rate was 157/100 person-years under UPS and 134 under ITPS. Protective efficacy was 61% under fully lined ITPS shelters, and 15% under roof lined ITPS alone. Anemia rates improved under ITPS in both camps. Burns et al [21] concluded that "this novel tool proved to be a

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convenient, safe, and long-lasting method of malaria control when used as a full shelter lining in an emergency setting". Of note Burns et al [21] observed great difference of ITPS on walls + ceiling *versus* ceiling only at *P. falciparum* incidence rate level. Diabate et al [28] found similarly significant entomological difference in experimental huts of Burkina Faso lined with permethrin treated plastic sheeting on walls only or walls + ceiling reporting that "ITPS had a major effect on the mortality of mosquitoes, the proportion killed being dependent upon the surface area covered" and "deterred entry of mosquitoes and inhibition of blood feeding were also correlated with surface area covered."

2.5. New tools for LNs

2.5.1. Combined LN with PBO or two different class of insecticide

Pyrethroid treated LNs are the principle tool upon which malaria control has relied for the last decade, however, the rapid ongoing spread of pyrethroid resistance in Africa, is likely to increasingly compromise their protective efficacy. This concern has highlighted the urgent need to develop alternative active ingredients for LNs. While a study on bitreated (OP or C + pyr) [29] nets showed positive results they have not been commercially developed or operationalised due to safety concerns. To tackle the issue of pyrethroid resistance a new model of LLIN call "Permanet 3" (P3) was recently developed by Vestergaard Frandsen SA, Aarhus, Denmark [30] with *a top panel* made of monofilament polyethylene fabric incorporating deltamethrin (121mg/m^2) and PBO (759mg/m^2) plus side panels made of multifilament polyester fabric coated with a wash-resistant formulation of deltamethrin (85mg/m^2) (while the usual concentration was 55 mg a.i./m^2 in classical Permanet 2 and 25 mg a.i./m^2 in former hand treated nets "ITN"). PBO is the synergist of pyrethrins and pyrethroids without intrinsic insecticidal activity. The action of the synergist PBO is due to inhibition of oxidative enzymes in the insect which can detoxify the insecticide (metabolic resistance). The inhibition or blocking of the detoxification enzyme significantly increases mortality of resistant insects. PBO is used in a ratio ranging generally from 3 to 8 with the active ingredient used, depending on the type of formulation and target insects. LLIN "Permanet 3" (P3) was recently tested in several countries of West, Central [31] and East Africa such as Tanzania [32] and Ethiopia [33].

In southern Benin, N'Guessan et al [11] tested LLIN Permanet 3 against *An. gambiae* M molecular form (highly resistant owing to knockdown resistance (*kdr*) site insensitivity and elevated oxidase and esterase metabolic mechanisms) and *Cx. quinquesfasciatus,* and showed that in experimental huts "the level of personal protection against *An. gambiae* biting from PermaNet 3.0 (50%) was similar to that from PermaNet 2.0 (47%)" and "protection fell significantly after 20 washes to 30% for PermaNet 3.0 and 33% for PermaNet 2.0".

In Côte d'Ivoire, in experimental huts of Yaokoffikro where *An. gambiae* population is mainly composed of S form (90%) *versus* M form (10%) and is strongly resistant with high *kdr* frequency (94%) and Cyt P 450 metabolic resistance, Permanet 3 (unwashed and washed 20x) were compared against the standard Permanet 2 (unwashed and washed 20x), and hand treated ITNs ("CTN") with K Otab® (washed 5x), with untreated nets as control [34]. It appeared that both unwashed and washed P3 reduced entry rate (- 60%) and increased exit rate as well as

other treated nets. On the other hand "a significantly higher mortality rate of *An. gambiae* s.s was recorded for unwashed PermaNet® 3.0 (55%) than for unwashed PermaNet® 2.0. However, for washed nets, there was no statistical difference between the mortality rates of *An. gambiae* s.s for washed PermaNet® 2.0, washed PermaNet® 3.0 and the CTN. Classical cone bioassays were conducted with the same nets (testing side panels and roofs) using either susceptible Kisumu strain of *An. gambiae* or local wild resistant population. Against Kisumu strain, all treatments including the washed CTN showed a mean KD rate over the threshold of 95% and a mean mortality rate >80%, (the official cut off).

Against pyrethroid-resistant wild caught *An. gambiae* s.s cone bioassays showed a mean KD rate < 95% and a mean mortality rate < 80% for all treatment arms, except with a mean KD of 94.3% and 98.6% and a mean mortality rate of 93.5% and 99.5%, respectively on side and roof showing a great efficacy even against polyresistant populations. The unwashed PermaNet® 3.0 gave the best results (KD 95.8% and mortality 97.0%)

In Tanzania, laboratory and experimental huts trial compared PermaNet 3.0 (P3), PermaNet 2.0 (P2) and a conventional deltamethrin treated net [32] against pyrethroid susceptible *An. gambiae* and pyrethroid resistant *Cx. quinquefasciatus*, (elevated oxidase and *kdr* mechanisms), Bioassays tests showed that against the susceptible *An. gambiae* P3 and P2 were still efficient after 20 washes while conventionally treated nets lost its efficacy. Against the pyrethroid resistant strain of *Cx. quinquefasciatus* Masimbani strain, it clearly appeared that the treated roof (with PBO) was much more efficient than sides (without PBO) of the LLIN. In experimental huts, general results of P3 and P2 (washed and unwashed) were comparable against pyrethroid susceptible *An. gambiae* and pyrethroid resistant *Cx. quinquefasciatus* and gave high similar personal protection. Mortality induced by unwashed P3 on resistant *Cx. quinquefasciatus* was higher than P2 (both washed and unwashed) and 20x washed P3, showing the increased efficacy achieved by PBO against pyrethroid resistant mosquitoes but this efficacy disappeared after 20 washes. Chemical concentration of the P3 roof decreased from 136 mg a.i./m^2 to 132 mg a.i./m^2 after 20 washes; whereas deltamethrin concentration of the P3 sides decreased from 103-109 mg a.i./m^2 before washing to 53 mg a.i./m^2 after 20 washes. The concentration of PBO decreased from 1142 mg/m^2 before wash to 684 mg/m^2 after 20 washes. Finally, chemical concentration of deltamethrin in P2 decreased from 61- 77 mg a.i./m^2 to 25 77 mg a.i./m^2 after the classical 20 washes.

Tungu et al [32] observed that "the tunnel tests demonstrated a synergistic interaction of PBO and deltamethrin on roof netting against susceptible *An. gambiae* and both susceptible and resistant *Cx. quinquefasciatus* relative to netting from side panels treated with deltamethrin alone. This synergy was manifested in higher mortality, reduced passage through the holes and reduced feeding rates with netting treated with PBO-deltamethrin. The synergy in tunnels against pyrethroid resistant *Cx. quinquefasciatus* was progressively lost over 10 washes and fully lost after 20 washes. Cone bioassays on resistant *Cx. quinquefasciatus* confirmed the loss of synergy over 20 wash".

Sumitomo have also recently released a new LLIN (Olyset Plus®) treated with a combination of permethrin and PBO, and they claim similar increased efficacy against resistant strains of

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mosquitoes. However, questions do remain about the efficacy of adding PBO and its impact on the development of resistance amongst mosquitoes [35].

2.5.2. New kit: New formulation and binder for long lasting treating net

The efficacy of the long-lasting treatment kits ICON® Maxx (Syngenta) (slow release 10% capsule suspension formulation of lambdacyhalothrin + a polymer binding agent) was evaluated under laboratory conditions and in an experimental hut trial in various situations [36].

Laboratory and field trials were recently implemented in central Côte d'Ivoire, where *Anopheles gambiae* s.s. are resistant to pyrethroid insecticides [37]. In laboratory studies, classical bioassays were conducted on Kisumu SS susceptible *An. gambiae* strain, with polyester and polyethylene nets with up to 20 classical washes. Unwashed the treated polyester net resulted in 89% KD and 52% mortality while the polyethylene treated net achieved 98% KD and 46% mortality. Washing these nets had a serious negative impact on efficacy, in terms of both KD at 1 hour and mortality at 24 hours. After 20 washes, KD rates dropped to 59% with polyethylene and 55% for polyester net i.e. below the mean KD defined for LLINs by WHO Pesticide Evaluation Scheme (WHOPES) guideline (i.e. 95% after 20 washings). After 20 washes the mean mortality also decreased for both netting materials to around 20%, falling well below the WHOPES criteria for long-lasting nets (KD ≥ 95% and/ or mortality ≥ 80% for at least 20 standards WHO washes under laboratory conditions using an *An. gambiae* Kisumu-susceptible strain). Field evaluation of 2 ICON Maxx polyester treated nets and 2 untreated ones (= control) was carried out over one year in the experimental huts of M'bé. The wild *An. gambiae* population (mainly S form, 92%) used in these studies showed a high frequency of *kdr* (# 97% pyrethroid resistant heterozygotes) with 2 ICON Maxx polyester treated nets and 2 untreated one (= control). Blood feeding rate was reduced and mortality was significantly increased (70% for 8 months) in huts with treated nets even against the resistant wild *An. gambiae* population. It is worth noting this impact on insecticide resistant *An. gambiae* population and further epidemiological studies should be carried out.

2.6. New non chemical approaches of larviciding

2.6.1. New formulations of entomopathogen fungus

Laboratory and field bioassays have been implemented "to develop formulations that facilitate the application of *Metarhizium anisopliae* and *Beauveria bassiana* spores (to improve spreading) for the control of anopheline larvae [*An. gambiae* and *An. stephensi*], and also to improve their persistence under field conditions" [36]. These studies showed that the pathogenicity of dry *M. anisopliae* and *B. bassiana* spores against *An. stephensi* larvae is however too short (# 5 days) to have any application in control settings; with ShellSol T fungal spores only somewhat more persistent. In field bioassays (Western Kenya), the percentage of pupation observed in *An. gambiae* larvae treated with ShellSol T formulated spores was much lower than with unformulated treatment: 43 to 49% with *M. anisopliae* and 39 to 50% with *B. bassiana* (at 10 mg and

20 mg respectively). Bukhari et al [38] suggest that "these formulated fungi can be utilized in the field, providing additional tools for biological control of malaria vectors".

2.6.2. Another new class of product: Spinosad

Spinosad has been considered as "a new larvicide against insecticide-resistant mosquito larvae" [39] representing a new class of insect control products [40] and it has been tested in several trials [41].

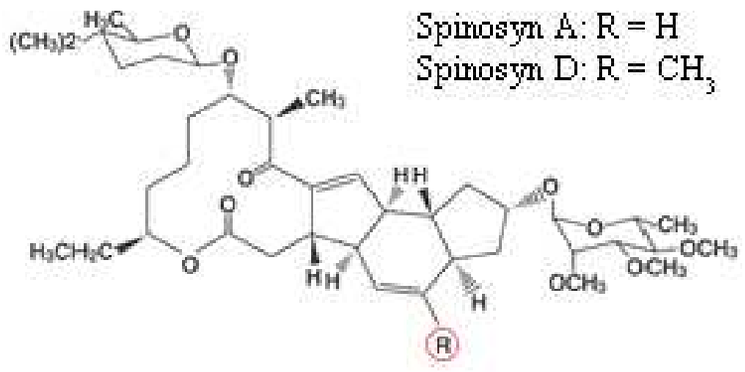

Figure 8. Two toxins of spinosad (Spinosyn A and Spinosyn D).

Spinosad is a fermented product derived from the mixture of two toxins (A and D spinosyns; Figure 8) secreted by soil based bacteria, *Saccharopolyspora spinosa*. It is traditionally used for crop protection [36] against pest insects. In the European Union, the active substance is included in Annex I to Directive 91/414/EEC by Directive 2007/6/EC and the rate of the pesticide residues in food is regulated in Europe. In France, the active substance is authorized for use in approved market products.

Spinosad acts on the nervous system of insects, by external contact or ingestion. It induces involuntary muscle contractions, prostration with tremors and paralysis. An insect stops feeding and paralysis may occur within minutes after ingestion of the product, death ensuing within one to three days. Spinosad has low toxicity to mammals, birds, fish and crustaceans but it is highly toxic to bees and aquatic invertebrates [42]. Spinosad (Group 5 insecticide) when used as a larvicide could be considered in rotation with another insecticide from a different class of pesticides.

Laboratory larval bioassays of spinosad on *Aedes aegypti*, *Cx. quinquefasciatus*, and *An. gambiae* (specimens that were either susceptible or resistant to pyrethroids, carbamates, and organophosphates) have shown that this product has a lethal action (mortality after 24 h of exposure) regardless of the original status, susceptible or resistant, of the mosquito larvae and was significantly more effective against *An. gambiae* than against the two other species and more effective against *Cx. quinquefasciatus* than *Ae. aegypti* [39] (Table2).

species	status	LC_{50}	LC_{100}
An. gambiae	SS	0.01	0.032
	RR (*Kdr*)	0.011	0.073
Cx. quinquefasciatus	SS	0.093	0.49
	RR (Ace-1^R)	0.12	0.59
Ae. aegypti	SS	0.35	0.92
	RR (*Kdr*)	0.32	0.72

Table 2. LC50 and LC100 of spinosad for *An. gambiae*, *Cx. quinquefasciatus*, and *Ae. aegypti* (SS, homozygote susceptible, RR: homozygote resistant).

Several other studies showed the potential of this bioinsecticide against different genera and species of mosquitoes [41, 43-44]. Different concentrations of spinosad were tested against larval instar and pupa of *An. stephensi* [45]. It was observed that "the reduction percentage of *Anopheles* larvae was 82.7%, 91.4% and 96.0% after 24, 48, 72 hours, respectively, while more than 80% reduction was observed after 3 weeks". A CS Spinosad formulation was tested in classical laboratory bioassays and successfully used for the control of *Ae. aegypti* and *An. albimanus* larvae in Mexico [46]. A spinosad shows an absence of cross resistance with insecticides commonly used in Public Health and it may be an interesting product to integrate into vector borne diseases control strategies where vectors are resistant to current insecticides.

3. Other new paradigms

3.1. Slow Acting Product (SAP) — Entomopathogens fungus

A completely new paradigm in vector control would be *slow acting pr*oducts called «Late Life Acting products » [47]. As malaria parasite sporogonic development last at least 10 days, any product which kills mosquito vectors within that time frame will automatically reduce the number of infected vectors and therefore almost certainly also reduce *Plasmodium* inoculation rates.

Formulated as biopesticides, fungal entomopathogens may have a great potential for application in indoor residual spraying of house wall surfaces or other resting places in human or animal dwellings. Once infected the fungus physically proliferates within the insect and results in the production of various secondary metabolites that have negative impacts on insect physiology [48-49] and performance and eventual death [50]. Histopathological studies of tissues infected by fungus suggest that the insect dies due to the combination of nutrient depletion, mechanical damage, and toxicosis. These biopesticides, if they can be successfully applied, could be useful for malaria control [51-52] especially if they prove effective against insecticide-resistant mosquitoes [53-55].

3.1.1. Entomopathogen fungus on clay

In recent trials [56] adult females of *An. stephensi* mosquitoes were exposed with cone tests to clay tiles sprayed with an oil formulation of spores of the entomopathogenic fungus *Beauveria bassiana* using different concentrations or time of exposure. A mortality rate of 100% was observed in less than one week, even when no KD effect was observed.

In addition to reducing longevity, it was noticed that fungal infection also reduces feeding propensity and fecundity [56-57] which added to the reduction of longevity could have a significant impact on vectorial capacity and therefore also on malaria transmission. Blanford et al [56] showed that "fungal exposed mosquitoes showed a declining response to the feeding stimulus over time, with 77, 60 and 50% of mosquitoes initiating feeding behaviors on days 1, 2 and 3, respectively and no mosquitoes responding on day 4. Combining the proportion of mosquitoes alive with the proportion attempting to feed gives a measure of overall transmission blocking (biting risk) on any given day. For treated mosquitoes, this combination of pre-lethal and lethal effects revealed reductions in biting risk of 36, 52, 72 and 100% on days 1–4, respectively. This represents complete transmission blocking within a feeding cycle".

Fungal infection was also observed to have a negative impact on flight performance which may be an important consideration for malaria control at focal level. Another very important character of entomopathogen fungus is its ability to control insecticide resistant mosquito strains. Exposure to the fungal biopesticide on clay tiles using the standard dose and a 30 minute-exposure period before classical bioassay (WHO cone test) of colonies of 3 species, *An. gambiae s.s., An. arabiensis* and *An. funestus*, (ranging from fully susceptible to resistant to DDT, and/or Bendiocarb, and/or Malathion, and/or Deltamethrin) showed 100% mortality by day 6 irrespective of mosquito species or the level of resistance to insecticides. Blanford et al. [56] who reported that "the *An. gambiae* colony ''TONGS'', which was fully resistant to all chemical classes, had an Median Lethal Time (MLT) of 4 (3.93–4.07) days and all individuals were dead by day 5 (± 0.0) which was not dissimilar to the fully susceptible *An. gambiae* colony ''SUA'' which had an MLT of 4 (3.82–4.18) days and were all dead by day 6 "(±0.25)". It clearly appeared that "insecticide resistance confers no cross resistance to fungal pathogens in the key African malaria vectors" and this point must be taken into account in the management of insecticide resistance. For Blanford et al [56] "what is striking here is that when the effects of blood feeding are added in, risk of malaria transmission is essentially reduced to zero within a day of fungal exposure and never recovers".

3.1.2. Entomopathogen fungus on nets

Howard et al [58] implemented several classical tube bioassays to compare the fungal-susceptibility of an insecticide-resistant (VKPER) and insecticide-susceptible strain (SKK) of *An. gambiae* and test the activity (and longevity) of *M. anisopliae* and *B. bassiana* conidia on white polyester netting (Table 3). It appeared that *M. anisopliae* and *B. bassiana* significantly increased mortality of both resistant and susceptible strains of *An. gambiae* exposed to 2 or 7 days after treatment of nets (Table 3). *B. bassiana* was significantly more pathogenic than *M. anisopliae* both for SKK and VKPER (Table 3). The insecticide-resistant mosquito strain VKPER was significantly more susceptible to fungal infection than the SKK strain after exposure to 2 or 7

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days after treatment of nets (table) while other studies did not find any difference in efficacy of dry conidia of *B. bassiana* on resistant or susceptible strain. It is possible that the discrepancies in data could be due to the mode of formulation of conidia (dry or ShellSol T suspensions in this study). The mosquito pathogenicity was maintained seven days after net application, but the viability of the two fungal species after seven days at 27°C was low, 62% and 2% respectively, for *B. bassiana* and *M. anisopliae,* hampering their practical application in LLINs.

		Days after treatment	
Fungus	*An. gambiae* strain	2	7
M. anisopliae	SKK	3.2	2.6
	VKPER	17.1	29.9
B. bassiana	SKK	11.0	7.4
	VKPER	32.2	43.5

Table 3. Comparison of mortality rates of fungal-susceptibility (*M. anisopliae* and *B. bassiana*) between an insecticide-resistant (VKPER) and insecticide-susceptible strain (SKK) of *Anopheles gambiae*.

Trials of entomopathogen fungus on mosquitoes have generated various results according to the protocol followed: formulation of fungus (dry/suspension); substrata (mud wall, cloth etc); field/lab trials; doses, exposure times; species of fungus; species/strain of mosquitoes, etc. Of note, Howard et al [58] successfully demonstrated the efficacy of nets treated with *B. bassiana* and tested against a resistant strain of *An. gambiae*. Even though the residual efficacy duration was short, the authors logically concluded that "Field trials over a longer trial period need to be carried out to see if wild insecticide-resistant mosquitoes are as susceptible as the colony strain used in this trial". Further studies, against resistant *An. gambiae* VKPER strain showed that "*B. bassiana* infection caused significantly increased mortality with the daily risk of dying being increased by 2.5 × for fungus-exposed mosquitoes compared to control mosquitoes. However, the virulence of the *B. bassiana* conidia decreased with increasing time spent exposed to the tropical field conditions, the older the treatment on the net, the lower the fungus-induced mortality rate. This is likely to be due to the tropical climate because laboratory trials found no such decline within the same trial time period. Conidial viability also decreased with increasing exposure to the net and natural abiotic environmental conditions. After 20 days field exposure the conidial viability was 30%, but the viability of control conidia not exposed to the net or field conditions was 79%" [59].

3.1.3. Influence of temperature

Kikankie et al [55] did several trials "to assess the susceptibility of insecticide-susceptible ("MBN") and resistant ("SENN") laboratory strains and wild-collected *An. arabiensis* to infection with the fungus *B. bassiana* under two different laboratory temperature regimes (21 ± 1°C or 25 ± 2°C)".

It appeared that exposure to dry *B. bassiana* spores resulted in significant reductions in longevity of the wild *An. arabiensis* mosquitoes and virulence was significantly higher at 25°C than 21°C, and exposure to *B. bassiana* spores resulted in significant reductions in longevity in all mosquito colonies regardless of their insecticide susceptibility levels and temperature regimes. Fungal susceptibility was not affected by resistance to insecticides.

It was also noted that "fungus-induced mortality rates were relatively rapid at 25°C, with 100% mortality taking 10-12 days post-fungus exposure in the baseline colonies (MBN and SENN) and field-collected mosquitoes" i.e. a lapse of time shorter than the duration of the sporogonic cycle of *P. falciparum* at this temperature, an important element for actual reduction of malaria transmission through vector control.

3.1.4. Influence of physiological stage and age

Mnyone et al [60] conducted bioassays using fed and unfed adult females of *An. gambiae* maintained in colony for several years with two fungal isolates: *M. anisopliae* and *B. bassiana* I93-825. Mosquitoes were exposed to conidia for 6 hours, with a follow up of 28 days. To study the effect of age, "three different age groups of female mosquitoes were exposed to both fungal isolates (2–4 days, 5–8 days, and 9–12 days post emergence), whereas to study the effect of physiological stage, five groups with differing blood-feeding status were exposed to both fungal isolates (non-fed, 3, 12, 36, or 72 h post-blood feeding). Results showed that, with both fungus, "older mosquitoes died relatively earlier than younger ones" and "blood-fed mosquitoes had a lower risk of dying relative to unfed ones". Increased risk of death in older than younger individuals has also been reported elsewhere [61-62]. Mnyone et al [60] considered that "the fact that blood-fed mosquitoes are less susceptible to fungal infection could be beneficial in terms of evolution proofing against resistance development. Although fungal infection reduces the fecundity of female mosquitoes [57], they are still able to pass their genes to the subsequent generation reducing selection pressure on resistance against fungi [55]. Furthermore, fungal infections suppress the successful development of *Plasmodium* parasites in the vectors [51], and hence both effects (i.e., fungus-induced mortality and parasite resistance) lead to a significantly reduced parasite transmission risk".

3.2. Attractive Toxic Sugar Bait (ATSB) methods

Recent studies on sugar feeding behavior of *Anopheles* [63-73] have been conducted in order "to optimize strategies for malaria vector control in Africa using attractive toxic sugar bait methods" [74] and to develop a new approach for mosquito control [75-78]. Stone et al [79] developed "an effective indoor mesocosm for studying populations of *An. gambiae* in temperate climates" and used the mesocosm concept to "determine whether the sugar-or-blood meal choice of *An. gambiae* females one day after emergence is influenced by blood-host presence and accessibility, nectariferous plant abundance, and female size" [80].

Stone et al. [80] noted that with a sleeping human present in the mesocosm, the majority of one day-old females obtained a blood meal. This was the case even with treated mosquito net use. But when a blood host was not present, or access was restricted through the use of a net,

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sugar meals became more frequent. The feeding choices of female *An. gambiae* were determined to a great degree by the presence and accessibility of the blood host, and not by the abundance of potential nectar sources in the mesocosm. Concerning the use of sugar baits as a malaria vector control, the strong tendency to feed on blood, even at one day post-emergence, suggests that in areas where larval development sites are close to human habitations, the method may be useful mainly as a complement to mosquito nets. If larval development sites are located at considerable distance from humans, the dominance of blood feeding is a smaller issue. Though females are willing to feed on humans as early as 24 h after emergence, in nature they may not come into contact with humans that early, and attraction to sugar sources would be paramount. Males and small females are particularly likely to seek a sugar meal when access to blood hosts is restricted by mosquito nets, suggesting that a plant-based method may be an effective control tool for such endgame scenarios. The combination of sugar baits (for instance, placed indoors or near a house) and treated mosquito nets, is one of these options. Its feasibility will require bait substantially more attractive than the plant species used in this experiment, such as the one used in Mali [78].

Based on highly successful demonstrations in Israel [75-77, 81] that attractive toxic sugar bait (ATSB) methods can decimate local populations of mosquitoes, Muller et al [78] implemented a study "to determine the effectiveness of ATSB methods for malaria vector control in the semi-arid Bandiagara District of Mali, West Africa". The *Anopheles* vector population was mainly composed of *An. gambiae* s.l. (mainly *An. gambiae* s.s. 86% and *An. arabiensis* 14%) and *An. funestus* [82]. The *Attractive Sugar Bait* (ASB) was composed, among other, by Guava (30%) (*Psidium guajava*) and honey melons (30%) (*Cucumis melo*) highly present in the area of the trial and known to be attractive for *An. gambiae s.l.* [83] while "ATSB was made by adding the boric acid [84-85] 1% (W/V) to ASB liquid". The ASB (in "control areas") and ATSB (in "treated areas") solutions were sprayed on the vegetation around the ponds and rice paddies and mosquitoes collected by CDC Light Traps at fixed positions between the ponds, during the 38 days of the trial, implemented at the end of the peak of malaria transmission period. It was observed that "ATSB treatment reduced densities of female and male *An. gambiae* s.l. by about 90%. After spraying ATSB in the treatment site, population densities of female and male *An. gambiae* s.l. declined rapidly over a week and then stabilized at low levels"; this impact on males is worth underlining as it could have an impact on decreased fertilized females and therefore on progeny. Furthermore, "ATSB treatment correspondingly affected the longevity of female *An. gambiae* s.l."

According to their data, Müller et al [78] considered that "ATSB methods differ from, and potentially complement, LLIN and IRS methods. In terms of malaria vector control in Africa, the ATSB methods when used operationally will likely reduce both total numbers of recently emerged female anophelines before they enter houses to feed on humans, and the proportion of females exiting houses to oviposit and then returning to houses to re-feed on humans. It is likely that ATSB approaches could soon be added as a major component of Integrated Vector Management (IVM) based malaria vector control programs" [86-88].

Along with their studies in Mali on the attractiveness of various local plants, fruits, flowers to mosquitoes *versus* human scents, Müller et al [83] noticed a very interesting "different rhythm

of attractivity as plants showed peaks of *An. gambiae* s.l. attraction between 19:30-22:00 and 04:00-05:00, which differed considerably from the response to human odors, which peaked at around midnight". The well-known local *Acacia macrostachya* and *Acacia albida* (Fabaceae) appeared very attractive, and *Hyptis suaveolens* (Lamiaceae) appeared highly repellent.

It is clear that a great lot of questions still remain to be solved about ATSB such as, among others: What is the side effect of spraying vegetation on non-target fauna? What is the actual epidemiological efficacy in various epidemiological settings? Which attractant is the best in different ecological and entomological conditions? Which "toxin" is the most effective in various entomological conditions? And should it be used inside as well as outside and following which method and what about the acceptability and actual community participation, etc?

Nevertheless ATSB is another interesting approach worth further study for potential use, in complement to other classical methods such as IRS and LLIN, to reduce the number and the longevity of vectors i.e. malaria transmission and hence incidence of parasite infection and malaria morbidity.

3.3. New mathematical modeling of impacts of vector control

Since Roos and Macdonald, many mathematical models have been developed [89-90] for example (Figure 9):

- to evaluate the influence of environmental variables (climate, rain, relative humidity etc) [91];
- to facilitate the mathematicians to further develop suitable models and help the biologists and public health personnel to adopt better understanding of the modeling strategies to control the disease [92];
- to evaluate the potential mortality impact achievable by different long lasting, insecticide-treated net delivery strategies [93];
- to develop "a novel, convenient and versatile method to model *Plasmodium falciparum* infection that accounts for the essential in-host processes: parasite replication and its regulation by innate and adaptive immunity" [94];
- to improve malaria elimination strategies in areas where data are still scarce or not fully reliable [95];
- to develop a flexible and user-friendly *website* with an online mathematical model of malaria elimination that is being developed interactively with end users [96]; the website can be accessed at http://www.tropmedres. ac/elimination (see Malaria Elimination Model. http://elimination.tropmedres.ac and Internet Model of Malaria Elimination User Guide http://www.tropmedres.ac/images/modelling/userguide.pdf;
- to inform resistance management practices [97] determining the impact of different mosquito control intervention strategies including the protection conferred by mosquito nets [98];

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- to develop new approaches such as the idea of evolution-proof insecticide [99-100].

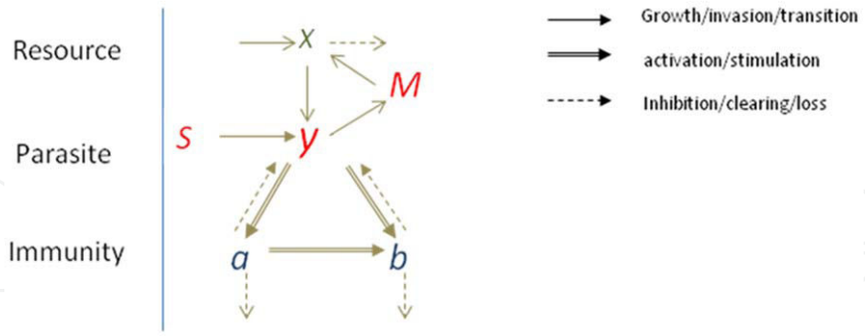

Figure 9. Schematic representation of model. The population of uninfected red blood cells (x) provides the source for the infected population (y). Level I immune effector (a) is stimulated by y. Level II immune effector (b) is stimulated by y interacting with a+b. M represents the number of merozoites, S represents an external source of inoculation

Mathematical models are useful in exposing what may otherwise be non-intuitive results, for example indoor residual spray (IRS) of insecticides in conjunction with mosquito nets can show antagonism, arising via interference of their modes of action while it is generally assumed that the two tools have synergistic benefits in reducing malaria transmission [101]. However, few have considered the spread of resistance in a variable selection pressure context [102]. A mathematical model [35] was recently developed to explore the effects on mosquito populations of spatial heterogeneous deployment of insecticides, to predict changes in mosquito fitness and resistance allele frequency, to identify important parameters in the evolution of insecticide resistance, to examine the contribution of new generation long-lasting insecticidal mosquito nets, that incorporate a chemical synergist on the roof panel, in delaying insecticide resistance.

Four niches were considered:

- Insecticide free (n): it can be an area either inside or outside a household;
- Non public-health related insecticide deployment: typically insecticide use in agriculture and households. These are deployed outwith of public health mosquito control campaigns, and generally out of the control of public health officials; mosquito coils, would also be included in this class;
- Insecticide-treated mosquito nets (ITN);
- Insecticide-treated mosquito nets with synergist on the top of the net (ITN + Synergist).

It appeared that resistance spreads slower in the presence of a synergist. The effect of synergist in males and females was not strictly comparable but was overall similar. The delay in the spread of resistance caused by the synergist was not very large; however, in approximately 10% of cases the rate of allele spread was higher when the synergist was fully effective. The predicted frequency of the resistance allele under different values of k at generation 70, the predicted frequency when the synergist is inefficient (k = 1), is 0.11 and when is fully effective (k = 0) is 0.26. The synergist has only a small impact in controlling the population, but even

small values of *k* will help to recover the effect of the insecticide, and this is may be the main contribution of the synergist. Nevertheless adding synergists to mosquito nets does decrease the rate at which resistance spreads in about 90% of scenarios. If a fully effective synergist ($k = 0$) is present, the fitness of all genotypes inside the house will be zero (*k* affects the 3 genotypes equally, so all mosquitoes die irrespective of their genotype) and the next generation will be mostly composed by progeny of survivors from the niche outside the household where selection for resistance was high. One hypothesis is that in this particular case the synergist removes the refugia of weak selection in the house thereby magnifying the effects of selection for resistance outside the house.

According to Barbosa and Hastings [35], "The finding that a situation can arise in which having a fully effective synergist in place contributes to intensify the spread of resistance is the most interesting result of this work, a very important fact often overlooked in modeling resistance: that it is highly dangerous to consider selection in only a single niche, isolated from other selection pressures, and to then extrapolate the results from the single niche to the whole population. In this case it seems reasonable to conclude that adding effective synergists will reduce selection for resistance in the household niche because all three genotypes are killed. The level of impact that a fully effective synergist could have on disease transmission is a question that cannot be directly answered by the results presented here, because it is not clear how the genetic concept of fitness translates into the demographic factors, such as mosquito population size and longevity that determine the intensity of disease transmission. On the other hand, as noted above, if synergist throws most of the selection pressure onto another niche then overall the rate of selection for resistance may increase. Consequently the impact of the use of insecticide within the home (predominantly as wall sprays and/or mosquito nets) on mosquitoes cannot easily be isolated from other insecticide applications that mosquitoes may encounter during their lifetime. This suggests that the malaria community is correct in being alarmed at the often uncontrolled use of insecticides in applications such as agriculture".

Ghani et al [103] developed a very interesting model to consider the possibility that a large reduction in malaria transmission may result in a loss of immunity, and how useful integrated malaria control measures could be to counterbalance such an eventuality. They prepared "a mathematical model for malaria transmission which incorporates the acquisition and loss of both clinical and parasite immunity", to "explore the impact of the trade-off between reduction in exposure and decreased development of immunity on the dynamics of disease following a transmission-reducing intervention such as insecticide treated nets". It is worth noticing how their model "predicts that initially rapid reductions in clinical disease incidence will be observed as transmission is reduced in a highly immune population. However, these benefits in the first 5–10 years after the intervention may be offset by a greater burden of disease decades later as immunity at the population level is gradually lost. The negative impact of having fewer immune individuals in the population can be counterbalanced either by the implementation of highly-effective transmission-reducing interventions (such as the combined use of insecticide-treated nets and insecticide residual sprays) for an indefinite period, or the concurrent use of a pre-erythrocytic stage vaccine or prophylactic therapy in children to protect those at risk from disease as immunity is lost in the population".

One of the key issues is the still current lack of sound knowledge about "malaria immunity" called "premunition" which involves immunity against the parasite, and therefore against the disease. For Ghani et al [103] "Clinical immunity develops over time dependent on the force of infection in the population and reduces the probability that an individual will develop clinical disease. Parasite immunity develops as individuals' age, and reduces the amount of time spent in the asymptomatic patent infection state (mimicking a reduction in parasite density and hence onward infectiousness)". Their previous model "suggests that the loss of both clinical and parasite immunity occurs over a period of years rather than weeks or months" [104] and according to a study in Madagascar, it seems that "immunity" could be of long duration [105]. In their model, Ghani et al [103] "assume that clinical immunity is developed at a rate proportional to the EIR in each setting and has a half-life of approximately 7 years and that parasite-clearance immunity has a half-life of approximately 14 years". They consider that 3 phrases are crucial: sustain intervention/integrated measures/sustain financial support and "Sustaining both control interventions and effective case management for many years, possibly decades, should remain the primary goal of all intervention programmes and it is essential that these long-term goals are matched with financial commitments".

3.4. New ecological care

Special attention is now devoted to the environment, especially environmental modifications that may result because of the impact of insecticides on the environment and its biodiversity.

3.4.1. Environmental Risk Assessment (ERA) and Insect Pest Management IPM

No pesticide is completely safe. Only through their careful use are we able to gain an understanding of the risks and control them. The environmental impact of biocides is generally studied in the context of scientific investigations conducted beyond the regulatory requirements for approval. This helps to generate better understanding of the biocides and provides opportunity to assess their potential impact and overall effectiveness when used in various control strategies. Although vector control methods are generally confined to urban and suburban areas, these areas may have a significant vegetation cover that provides both refuge and food for wildlife (insects, reptiles, birds, bats etc)...). This shows the need of environmental risk assessments prior to large scale vector control interventions. It also highlights the need for further studies to determine direct, indirect short and long-term potential effects. Risk assessment of control methods must be addressed in an integrated strategy taking into account the relationships between species in regards of the local biodiversity. In fact, environmental risk assessment of these treatments cannot be limited only to consider information on hazards, such as acute toxicity of the biocides used. Every effort needs to be made to minimize the use of chemical pesticides. A great deal of improvement can be made in vector control programs if the existing, methods and materials are more effectively used. The idea of integrated vector control which effectively combines a package of appropriate control methods i.e. insecticidal, environmental, biological and physical, in an orderly and coordinated manner can impact upon insect vectors and diseases with positive results of economic, ecological and sociological consequences [106].

Programs based on Insect Pest Management (IPM) must be designed to reduce vector bites and disease transmission, but also mitigate any potentially negative effects, i.e., such as environmental damage, harm of non-target organisms exposed to insecticides, or increase of insecticide resistant in target organisms [107]. Such programs do already exist notably in the USA (for example in Santa Barbara County) and in Australia [108]. In these programs, process are very well defined step by step: 1) vector surveillance and identification of target vector species to develop species-specific pest management strategies based on developmental and behavioral considerations for each species; 2) threshold measures to determine when action is necessary; 3) public education, control, prevention; 4) monitoring of efficacy and environmental impacts to identify the occurrence of unexpected/unwanted effects of treatments.

3.4.2. Impact of insecticides used for vector control

The impact of insecticides on the environment depends not only on the active substance, but also the formulation and the method of applying: indoor residual spraying, space spraying or treated nets will have different impacts.

3.4.2.1. Indoor Residual Spraying (IRS)

Domestic livestock (particularly chickens) and organisms in the environment may be harmed if operations, cleanup, and disposal are not conducted according to best practices.

Table 4 describes the potential ecological effects of each recommended IRS chemical. There is a lack of data concerning toxicity of IRS insecticides on non-target fauna. However, most insecticides are highly toxic for aquatic and terrestrial arthropods like bees (in particular pyrethroid), and some of them can also be toxic for mammals (some pyrethroids and organophosphates).

3.4.2.2. Space spraying and larviciding

Space spraying has only occasionally been used in malaria epidemic control program and as a complementary measure against exophilic vectors. Nevertheless, pyrethroids, which have a short remanence, have been the predominant insecticides [123], and then care must be taken to avoid applications near fish-bearing water bodies. It is also recommended that such applications should not be carried out directly over water bodies and that a no-treated barrier of 100 m should be maintained to prevent fish mortality. Home owners should be advised to cover domestic fish tanks and bird cages during the applications [123].

Blom [124] examined the effects of aerial, barrier, and ground based ultra-low volume (ULV) sprays with sumithrin and deltamethrin, in Massachusetts on non-target insects. Malaise traps, targeting the flying insect population, were collected in regular intervals before and after sprays, then the captured insects were sorted by order and counted. The results have shown little effect on non-target insects from the ground based sprays, and a temporary knockdown from the aerial spray. However, Coleoptera were affected in the short term by the ULV sprays and, suffered long term effects from aerial spraying.

IRS insecticides	Mammal	Bird	Fish	Aquatic invertebrate	Bee	References
α-cypermethrin	0	0	++	++	++	[109]
Bendiocarb	0	0	+	+	++	[110]
Bifenthrin	+	+	++	++	++	[111], [112]
Cyfluthrin	+	0	++	++	++	[113]
DDT	+	+	++	++	+	[114]
Deltamethrin	+	0	++	++	++	[115]
Etofenprox	0	0	+	+	++	[116], [112]
Fenitrothion	0	+	0	++	++	[117]
λ-cyhalothrin	+	0	++	++	++	[118]
Malathion	+	+	0	++	++	[119], [120], [112]
Pirimiphos-methyl	++	0	++	++	++	[121], [112]
Propoxur	++	++	++	++	++	[122]

Key: 0: non-toxic; +: potentially toxic; ++: highly toxic

Table 4. Toxicity of chemicals used for IRS on non-target organisms

Davis and Peterson [125] assessed long-term impacts of permethrin on non-target terrestrial arthropods after repeat ULV applications in the context of West Nile Virus Management in the USA. The authors concluded that although small flying insects that were active at the same time as mosquitoes were slightly impacted, effects on non-target arthropods exposed to adulticides applied via ULV sprayer would be small in the ecosystem studied.

Several classes of recommended larvicides are used in vector control management such as: the bio-insecticides (*Bacillus thuringiensis* var. *israelensis (Bti)*, *Bacillus sphaericus* (*Bs*) and spinosad), the organophosphates (chlorpyrifos, fenthion, pirimiphos-methyl, and temephos), and the insect growth regulators (diflubenzuron, methoprene, pyriproxyfen). The results of some studies concerning the environmental risk assessment of these larvicides are summarized in the Table 5.

3.4.2.3. Treated net

Long-Lasting Insecticide-Treated Nets (LLINs) have many important advantages as there is no need for re-treatment, the insecticide consumption is reduced, and release of insecticide in natural water bodies during washing is also reduced [142]. However, there is considerable misuse of mosquito nets for drying fish and fishing, in particular along Lake Victoria [143]. In their study, Minakawa et al. [143] surveyed 7 fishing villages along the lake and estimated that 239 LLIN were used for fishing and drying fish from the 1040 LLINs distributed by NGO in these villages. This could have an impact on aquatic organisms while the net are immersed into the lake water. On the other hand, LLIN can also moderately impact non-target household

Larvicides	Mammal	Bird	Fish	Aquatic invertebrate	Bee	References
Bti and *Bs*	0	0	0	0[a]	0	[126]
Spinosad	0	0	0	++	++	[127-129]
Chlorpyrifos	+	++	++	++	++	[130]
Fenthion	++	++	++	++	++	[131-132]
Pirimiphos-methyl	++	0	++	++	++	[133-134]
Temephos	+	0	+	+	++	[135-136]
Diflubenzuron	0	0	+	+	+	[137-139]
Methoprene	0	0	0	++	+	[134]
Pyriproxyfen	+	0	+	++	+	[140-141]

Key: 0: non-toxic; +: potentially toxic; ++: highly toxic

[a] In some cases non-target Nematocera such as Chironomidae can be impacted by *Bti*, depending on the dose and the formulations applied (Boisvert and Lacoursière, 2004)[126].

Table 5. Toxicity of larvicides chemicals on non-target organisms

pests such as house fly, American cockroach, head louse, and mosquito bug after 30-min exposure [144].

3.4.3. Environmental management

Mosquitoes breed in shallow-water habitats, so it is not surprising that most environmental management interventions for malaria control are associated with the manipulation of wetland environments. If applied correctly, these strategies can have very good results by modifying vector-breeding habitats [145]. But these habitats can include freshwater wetlands (swamps, flood plains, riverine forest, and swamp forest), mangroves, and coastal wetlands (lagoons, estuaries, and tidal mudflats) [146]. In some geographical regions, there are also semi-arid grasslands, which maintain areas of temporary flooding. Wetlands provide a wide range of ecological services including soil erosion and flood control, water purification and pollutant and nutrient retention, groundwater discharge and recharge, and provision of habitat and breeding grounds for wildlife. Disturbing wetlands through environmental management may alter the quantity and quality of the services that wetlands provide. Increasing water runoff (or, alternatively, a change in the composition or clearing of wetland vegetation by drainage or clearing vegetation) may also decrease the ability of the wetland to take up pollutants, potentially diminishing the quality of water resources. It may also cause higher peak water flows in streams and rivers during rain events, resulting in flood damage. Vegetation clearance may also decrease spawning ground for aquatic species and decrease breeding habitats for migratory birds and animals [147].

Larvivorous fish (such as *Gambusia*) are often introduced for biological control. However, the introduction of exotic fish species into the natural environment (e.g., wetlands and marshes)

could disrupt existing predator–prey relationships and alter ecosystem composition. In some cases, the introduction of *Gambusia* has led to the destruction of native fish [145].

3.4.4. Methodological approach for ERA in the context of vector control

Measurements of toxicity based on the impact of a chemical on a species of interest, such as the LC_{50} (concentration that kills 50% of a population), and the no observable effect concentration for reproduction, are used extensively in determining ecological risk. But these methods are too simplistic to establish relationship between the results obtained and the response observed [148] and are not always representative of real life settings. As a consequence, new assessment methodologies to predict and anticipate the risks associated with new chemicals, and improve knowledge about existing chemicals are needed. The last decade has seen some development in this area, but there have been very few studies on the effects of large scale vector control published [149]. Recently, indirect effects of *Bti* treatments on birds such as house martins *Delichon urbicum* have been shown via measuring impact on their insect food sources [150]. In this study, the authors have measured foraging rates and chick diet and have shown that clutch size and fledgling survival were significantly lower at treated sites relative to control. Their hypothesis is that intake of Nematocera (Diptera) and their predators (spiders and dragonflies) decreased significantly in the sites treated with *Bti*, hindering the breeding success of the house martins. Another study on *Bti* monitored Chironomidae populations [151] in three wetlands treated with *Bti*-treatment to control mosquitoes, and three untreated wetlands. Results showed no reduced production of chironomids in *Bti*-treated as compared to untreated wetlands. However, the same authors [152] identified possible indirect effects of *Bti*-treatments in a further study that showed a higher specific richness of chironomids in treated wetlands, compared to control wetlands. They hypothesized that this was the result of reduced competition from mosquito larvae.

These studies demonstrate the need for more suitable methodologies and protocols to be developed for long-term monitoring of ecosystems. Several studies in Europe have monitored long term mosquito control effects, including programmes efforts in western France [153-154], and another in Ramsar area of southern France [155] where the Life-Environment European Program has been studying methods for the sustainable management of mosquito control. The French Ministry for Ecology, Sustainable Development and Spatial Planning via the National Programme for Ecotoxicology (PNETOX; APR2003) are studying the harmonisation of mosquito control methods in terms of their impact on non-target invertebrates in Mediterranean and Atlantic coastal wetlands [156].

A Life-Environment project, sustained by the European Commission, called "Control of noxious or vector mosquitoes: implementation of integrated management consistent with sustainable development (IMCM/n° n°LIFE08 ENV/F/000488)" is also under way in France. Its objective is to validate integrated methodologies and techniques allowing (1) a precise and up to date knowledge of target species' presence, biology, colonized habitats, using GIS/GPS tools, (2) the development of control methods fully appropriate to the health and environmental risks faced, (3) an evaluation of nuisance thresholds based on knowledge of social demands through sociological surveys, in order to optimise the communication strat-

egies, (4) traceability of operations by means of retrospective and prospective analyses, and (5) the adoption of valid procedures and methodologies for the monitoring of the non-intentional effects on Man and the environment that can result from these control methods. This project will implement these decision-making tools with five public bodies that are involved in mosquito control efforts in Metropolitan France (Entente InterDepartementale pour la Démoustication du Littoral méditerranéen, EID Méditerranée, Entente InterDépartementale Rhône-Alpes pour la démoustication, EID Rhône-Alpes, General Council of Southern Corsica) and overseas (General Councils of Martinique and Guyana). The project prioritises environmental care and uses complementary methods for environmental risk assessment (in aquatic and terrestrial compartments) for mosquito control methods in temperate or tropical zones. All these projects have focused on consideration of the indirect possible effects of mosquito control on the invertebrates' communities in order to preserve the local biodiversity and endangered species. These projects have highlighted the importance of using methodologies adapted to the habitats and specific organisms, with relevant bio-indicators, implemented infield settings that represent the context in which the vector control management is to be undertaken. The studies also underlined the necessity of post-approval monitoring of the insecticides used in vector control management.

4. Conclusion — Discussion

The history of vector control for malaria control can roughly be divided in 3 main periods: before DDT: from general control to "eradication"; the DDT era and the "Malaria Eradication Programme" (MEP); after DDT: insecticide treated nets (ITN-LLIN), Integrated Vector Management (IVM) and new paradigms.

4.1. Before DDT

Since his discovery of the role of mosquito as vector of malaria parasite, Ross advocated the vector control for malaria control and in 1899, in Sierra-Leone; he "carried out the first project based on his discovery. His principal weapon was "illuminating oil" (kerosene)". It "was a transient success" not sustained due to lack of funds [157]. "In 1907 Ross was invited to Mauritius to organize antimalaria operations there. His recommendations were sound and the results were good if the government had given them more support" (Bruce-Chwatt, loc.cit.). It is interesting to underline some of the main issues observed at that time: the lack of financial and political support and the financial support is still matter of concerns when referring to the recent RBM statement. The greatest and most successful programme was malaria control in the Panama Canal zone by Gorgas [158] who, helped by Joseph Le Prince, successfully planned and implemented "*sanitation measures*" based on the principle to deal with the situation by all available means based on the role of mosquitoes. He could be therefore considered as the actual precursor of IVM.

Still underlined by Bruce-Chwatt (loc. Cit) "among the early projects one carried out by Malcolm Watson in Malaya deserves special mention, because of the ingenious combination

of open and subsoil-drainage with naturalistic methods of control of *Anopheles* [159]. These measures were adapted to the behavioral characteristics of malaria in a given area and formed the basis for the concept of "*species sanitation*" [160].

After the success of Watson, several other "naturalistic methods" were developed such as altering the salinity of breeding site of *An. ludlowae* control in Indonesia, introduction of natural enemies of mosquitoes, use of *Gambusia* in California, Florida, then in Cyprus, Spain, Italy, Russia, Chile, etc [161].

Some of the best example of environmental modifications based upon drainage for successful malaria control were observed in Italy with reclamation of marshy areas (with resettlement of population in new land) for "*bonifica integrale*" of Pontine Marshes of the Roman Campagna [162-164] or Algeria in the marshy area of Mitidja Plaine [165-166].

Such programs could also be considered as precursor in the field of biological control which currently received great attention with the ecological issues of insecticide and insecticide resistance of main vectors.

In term of chemical control, 2 schools of thought were opposed*:* larva control, based upon Paris Green dust successfully used in Sardinia and Calabria and in several other places such as Brazil to get rid of invaders *An. gambiae* which caused severe epidemics of malaria in 1930s'; and adult control, with the use of the well known oriental daisy *Chrysanthemum cinerariaefolium*, (used for long time as fumigants in China against biting insects) the powder made of it contains powerful insecticide compounds such as pyrethrins and cinerins and as soon as 1932 Park-Ross and De Meillon instituted systematic house to house weekly sprayings of pyrethrum solution in kerosene for the control of adults *Anopheles* in Natal and Zululand and this program is somehow still ongoing with the regular inside resting spraying (with DDT) operations added to case management to control malaria in KwaZulu Natal [167]. Instead of pyrethrins, National Malaria control programme uses now pyrethroid but they are chemically developed from natural pyrethrins used formerly. Somehow history of approaches for malaria control repeats itself.

It is interesting to notice the variety of approaches and techniques involved (species sanitation, sanitation measures, bonifica integrale (reclamation of marshy area and resettlement of populations on the new land), pursued by Italian governments for many years, larval control through different measures from source reduction to Paris Greendust spraying, adult control with spray of pyrethrin, …) based on some knowledge of entomological, ecological and socio-economical situation for improvement of Public Health, control of outbreak or achievement of large constructions (dams, Panama Canal, etc). In a way these measures paved the way for new approaches developed after the failure of the Global Malaria Eradication Programme and the development of IVM with new paradigms for vector control.

4.2. The DDT era 1957 — 1969: Global malaria eradication programme

"In 1874 a Viennese student of chemistry, Othmar Zeidler, published in the Berichtungen (Proceedings) of the German Chemical Society a paper under the title "Verdindungen von

Chlral mit Brom und Chlorbenzol"; the compound described in it was DDT (Bruce-Chwatt, loc cit) but its insecticidal properties remained unknown until 1939 [168].

The first Expert Malaria Committee (Ciuca, Gabaldon, Hamilton, Fairley, Pampana, Russell) met in Geneva in 1947 to deal with "the enormous social and economic damage that malaria was causing to the developing tropical countries", Russell [169] estimating that throughout the world there were some 300 million cases of malaria every year with at least a million deaths, it is interesting to underline that such evaluation of the burden of malaria was regularly reported during the following decades. And as Bruce-Chwatt [157] rightly underlined: "this was also the time when the new concept of malaria control by imagocidal measures was stimulated by the reports of the extraordinary properties of an obscure compound synthesized 65 years before the outbreak of the Second World War. They were observed by a Swiss chemist, Müller who was looking for a substance active against clothes moths, and with the biologist Wiesmann they realized in 1939 the insecticidal properties of this product, named Gesarol or Neocid and first used in agriculture [170] then sent to USA and Britain (where it received the acronym DDT). This product presented 3 important operational properties: long persistence of residues on sprayed surfaces; high toxicity for insects and low for man; killing insects by simple contact. The advent of DDT revolutionized malaria control as the residual indoor spraying as this product appeared simple, and could be successfully and economically used even in rural areas where malaria was the worse. Actually a lot of successful campaigns were done in Sardinia (Italy) (for eradication of *An. labranchiae*), Cyprus, Greece, Venezuela, British Guiana, Bombay State, etc [171]. In 1955, Pampana and Russell [172] underlined the needs of "plans to eradicate malaria from a territory within a few years, so that eventually the recurring item of malaria control could be struck from the annual budget". And the Eighth World Health Assembly in 1955 decided "that the World Health Organization should take the initiative, provide technical advice, and encourage research and co-ordination of resources in the implementation of a programme having as its ultimate objective the world-wide eradication of malaria".

DDT appeared as a "magic bullet" but the great mistake was that the original policy relied only on the use of residual insecticide, DDT then other organochlorines (BHC, dieldrin,...) along with drug use for reducing human reservoir, with the same strategy to be implemented everywhere without taking care of biodiversity, epidemiological diversity, social, economical, entomological diversity. The basic concept was one malaria and therefore one strategy to be implemented faster than insecticide resistance spreading, already noticed in the main vectors such as *An. gambiae*. In 1956, the Ninth World Health Assembly recommended the policy of eradication and stimulation of inter-countries cooperation. The strategy was defined as "operation aimed at cessation of transmission of malaria and elimination of the reservoir of infected cases in a campaign limited in time and carried to such a degree of perfection that, when it comes to an end, there is no resumption of transmission". It was based upon 3 successive steps: "attack phase" with total coverage with inside residual spraying, then "consolidation phase" to eradicate any remaining foci after the IRS rounds, then the "maintenance phase" where the malaria eradication programme doesn't exist as such and comes under the responsibility of general health services involves in "vigilance" to check any imported cases.

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During the following decades malaria was actually eradicated from Europe, part of Russia, Middle East, North America, Australia, Japan, Singapore, Korea, Taiwan, almost all West Indies Islands and about 53% of the population of the originally malarious areas became free of malaria. But "the magnitude of the malaria problem in Tropical Africa has been daunting" (Bruce-Chwatt, loc cit). A re-examination of the global strategy of malaria eradication was carried in the 60' and the results presented at the 22nd World Health Assembly in 1969. One of the conclusion was that "in countries where eradication does not appear to be feasible because of the inadequacy of financial resources, manpower requirements or shortcomings of basic health services, malaria control operations should move to a transitional control programme stage, with the aim of launching of an eradication programme in the future". This is political wording that recognizes the failure of the rigid Global Eradication Programme and the reality that this may translate to "malaria control" involving the use of every available effective method to tackle first malaria mortality and morbidity, rather than malaria transmission specifically, as it was targeted by the MEP.

After the illusion of the Malaria eradication came the time of pragmatism, and the recognition of the biodiversity concept with IVM which takes into account all biological but also economical, socio-cultural components of the vector-borne parasitic disease and tools available (or to be developed) to tailor vector control measures to each epidemiological settings, to reach its full efficacy in the aim of sharply reduce, then eliminating malaria steps by steps. In this concept of biodiversity, a flexible and multifaceted approach is requested and paradigms were developed accordingly. For example, it is generally considered that tools for vector control must have a quick action to kill vectors before they transmit the parasites to any other human being, but slow acting products are now envisaged considering that if life is shortening to become less than the duration of the sporogonic cycle there couldn't be any transmission of the pathogenic agent even if this takes slightly more time than the "killing" product. Another approach is to mix different products for LLIN or IRS to deal with insecticide resistance and even to join IGR usually used against larvae in product targeting adults such as insecticide paints and even LLIN. The main impact should therefore be observed in term of reducing fecundity and fertility which would impact new generations of adults and more generally *Anopheles* populations.

Nevertheless for the time being the only new tools operational for vector control at large is insecticide treated nets (ITN) currently industrialized treated to become Long Lasting nets and which clearly showed their efficacy if well used and maintained. But the field is largely open for new tools mainly dealing with insecticide, and sometimes social resistance.

A great attention is now devoted to the cultural and social aspects of vector control methods implemented from outside, the "non usage" or "mis-usage" of mosquito nets are good example of the misfit between International agencies which gave large number of LLIN free of charge and the local social acceptability or local financial constraints.

A great care is also given to ecological impact and Malaria control programme must take lessons from the large multicountries Onchocerciasis Control Programme for managing insecticide resistance and care of non targeted fauna.

We must keep in mind the sentences of late Prof Bruce-Chwatt [173]: "the present approach to the control of this disease envisages a progressive incorporation of all general and specific antimalarial activities into the primary health care structures. This opens up many possibilities for research on the use of different technical resources together with the involvement of indigenous communities. But this is a different story!".

List of abbreviations

ATSB - Attractive toxic sugar bait

ASB - Attractive Sugar Bait

C - Carbamate

CS - Microencapsulated formulation

CTN - hand treated ITN

DL - Durable wall linings

EID - Entente InterDepartementale pour la Démoustication

ERA - Environmental Risk Assessment

IGR - Insect Growth Regulator

IPM - Insect Pest Management

IRS - Indoor Residual Spraying

ITN - Insecticide Treated Nets

ITPS - Insecticide-Treated Plastic Sheeting

IVCC - Innovative Vector Control Consortium

IVM - Integrated Vector Management

KD - KnockDown

KDR - KnockDown Resistance

LC50 - median Lethal Concentration of a substance

LC100 - absolute Lethal Concentration

LiST - Lives Saved Tool

LLIN - Long-Lasting Insecticidal Net

LN - Long lasting insecticide treated Net

MEP - Malaria Eradication Programme

MLT - Median Lethal Time

OC - Organochlorine

OP - Organophosphate

P3 - Permanet 3

PBO - Piperonyl Butoxide

Pyr - Pyrethroid

RBM - Roll Back Malaria

SAP - Slow Acting Product

TPP - Target Product Profile

ULV - Ultra-Low Volume

UPS - Untreated Plastic Sheeting

WHO - World Health Organization

WHOPES - WHO Pesticide Evaluation Scheme

WL - Durable Wall Linings

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