# Insecticidal Bednets for the Fight Against Malaria – Present Time and Near Future

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**Abstract:** Malaria is to-day a tropical disease that especially has major impact in Subsahelian Africa. The current large-scale campaign against malaria focuses on better first line use of medication and prevention: (1) the combined use of an Artimisin derivative and one of several synthetic anti-malarials; and (2) the use of insecticidal bednets for transmission prevention, since the disease is transmitted between humans by female mosquitoes. The change from nets that were to be treated and often re-treated to factory pre-treated nets about 7 years ago, made the change from a promising research tool to a major campaign tool. However, once the first line problem of fast disappearance of insecticide treatment was solved, other problems appeared such as physical net durability and low use rate of bednets among people that do not see only the advantages of the nets, but also experience the inconvenience of their use in the daily life. Finally, resistance to insecticides is appearing, probably originating from agricultural use of the same insecticides, but now amplified by the extensive use of insecticides for malaria control. A call for use of common sense and diversified use of insecticides is concluded.

**Keywords:** Malaria, bednets, insecticides, mosquitoes, developing countries.

## INTRODUCTION

Malaria is a disease where the parasite has separate development stages in humans and in mosquitoes. One and a half centuries ago, malaria was a disease that was spread in most of the world, including Europe and US. Changes in house designs, use of screens and drying up swamps removed malaria from most of these northern areas, the final clean up was done with DDT after the Second World War. To-day, malaria is still a major cause of child mortality in Africa and an important disease and economic load in most tropical countries. The human malaria parasites all belong to the genus *Plasmodium* and all 5 species are spread by mosquitoes of the genus *Anopheles*. In humans, the parasite first invades the liver, then from there the red blood cells that are increasingly destroyed, eventually leading to anemia. The parasites modify our blood cells that leads to clotting and that again may block e.g. vessels in the brain and result in convulsions and eventual death. There are many other interactions between these parasites and the human host and not all are well understood. It is the sexual stage of the parasite that is transmitted to the mosquitoes when sucking from infected blood. These so-called sporozoits mate in the stomach of the mosquito, penetrate the mosquito gut wall to form an egg outside on the gut, then multiply to the infective stage that are injected into another human host about 10-14 days later. Since the mating of parasites occur in the mosquitoes, this is also where new, genetic recombinations are made. Therefore, preventing mosquitoes from biting is an important way to reduce malaria transmission and parasite diversity in a population.

The malaria disease can be cured. Quinine has been used for centuries and is still an effective treatment, but side effects can at times be very severe. It is originally a bark extract from the *Cinchona officinalis* tree. The synthetic chloroquine became a cheap and world wide used replacement that was also used in preventive treatments. However, resistance to chloroquine spread from Asia to the rest of the world and later on, resistance to many alternatives followed the same route. In the recent years, combination therapies combining a modified plant extract from *Artimisia annua (wormwood)* with a longer lasting effect of one of several synthetic antimalarials are introduced as effective treatments worldwide. However, effect of the artimisin derivatives have already started to deteriorate in the areas of SE Asia, where resistance to all former products also started, probably from the use of artimisin as single drug and under dosed.

Insecticide treated bednets (Fig. **1**) have been important tools to reduce morbidity and mortality in the Roll Back Malaria campaign. Their efficacy was first demonstrated for nets and curtains dipped in insecticide solutions and dispersions [1-3], but these tools were not yet practical. Getting insecticides and nets to the right place and at the right time was difficult, getting nets properly impregnated every 6 to 12 month even more. Finally, when people had to pay for the retreatment, retreatment rates fell below 5 % [4, 5]. Untreated, intact nets provide some protection, but as soon as they are holed, the protection disappears. The effect of the insecticide treatment is not only to protect the single user, but also often to prevent the mosquitoes to fly somewhere else to bite, because many will get killed by the net contact. World Health Organization (WHO) gave preliminary recommendations to the first types of long termed insecticide treated nets, Olyset in 2002 and Permanet in 2003 [6]. Compared to the nets for dipping, the ready-to-use insecticide treated net that resisted washings were a great leap forward.

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**Fig. (1).** Insecticide treated bednet.

The two first types of bednets were based on two fundamentally different technologies.

The long lasting insecticidal bednet was developed as a response to the problems with re-impregnations, and had several logistic advantages. Nongovernmental organizations (NGOs) and governments could now deliver nets only and did not have to deal with the concurrent distribution of insecticides (much more problematic), re-impregnation campaigns and financing of all this. However, as in any other development, once you solve one problem, new problems appear.

These were: (1) durability of net material and (2) the insecticidal effect; (3) coverage and use; (4) insecticide resistance.

Below, these four subjects will be discussed one by one starting with a characterization of some of the long lasting bednets seen in the light of product development and some of the problems seen in the field.

## CURRENT PROBLEMS WITH LONG LASTING BEDNETS

### Durability of Insecticidal Nets

Olyset® developed in the early 90's is made of polyethylene and has the insecticide incorporated into the yarn. This technology was previously used for making banana sacks to protect against insects during growth and early storage as well as in laminates to protect against termite attacks on constructions and of cables. The yarn used for Olyset is quite thick (declared to be 150 denier, but in reality nearly 200 denier; denier being the weight of 9000 m yarn) and made of HDPE (High Density Polyethylene). In addition to making the nets very strong this also makes them quite rigid with a distinct plastic-like feeling.

Permanet® was not different from the existing dipped nets except that the coating was made in a factory and included wash resistant chemicals as used in the textile industry for surface treatment of garments. Thereby, Permanet sought to address the problem of wash resistance, while keeping to materials already provided to the market cheaply and on a large scale. While Permanet achieved the 20 washes required to obtain WHO recommendation, it did not improve on the susceptibility to wear and tear of the old polyester nets. That problem was not yet in focus. Any net factory with standard equipment could run this type of production. Most products submitted for testing with the WHO since that time –failed or not – have therefore been of the polyester type.

Different brands of Long Lasting Insecticidal Nets have been developed to respond to the known problems of the two first. Duranet® from Clariant and Clark Mosquito Control is a polyethylene nets with a heavy yarn like Olyset, but with a smaller mesh size. This configuration addressed the problem that people fear mosquitoes will enter through the big holes in the open mesh of Olyset. This concern regarding mosquitoes entering through the mesh is correct in areas where one type of resistance is present: the Knock Down Resistance (kdr). Kdr provides reduced sensibility to the insecticide and delayed irritability and intoxication response, thus giving the mosquito time to enter through the mesh and bite before being affected [7]. Netprotect® is also a polyethylene net with a fine mesh, but is made with a thinner yarn. The polyethylene polymer is comprised of a mix of grades to obtain a softer net, which renders it less rigid than the Olyset while remaining strong. Both nets release insecticide from the core to the surface.

On the polyester side, the problem of net durability was attacked with a new version of Permanet. Permanet 3 was developed using a 75 denier yarn on the sides, but using an elastic knitting type instead of the traditional so called Raschel knitting. The upper part of the sides are knitted to a square meter weight as a traditional 75 denier polyester net (each hole about 2,5 mm in diameter), but has a lower strength than these as measured in bursting strength, probably due to the new knitting pattern. The lower part uses the same yarn, but is knitted tighter, thus more yarn per square meter and heavier. This part of the net has a weight per square meter as a net knitted with a traditional 100 denier in a traditional mesh, but is also found weaker than these in bursting strength measurements. Traditional 100 denier nets are also quite common on the market but it has not been demonstrated that they are much stronger in practice than the 75 denier net. If the change in knitting solves the problem of polyester net durability in reality has yet to be seen. For better mosquito control, the net has a roof in polyethylene that incorporates a synergist, piperonyl butoxide combined with deltamethrin. The purpose of this is to overcome some types of pyrethroid resistance. However, WHO studies have shown that this synergist has no significant effect and the nets are not different in effect from a standard Permanet [6].

The current situation of net durability is quite well described, but not included in net procurement guidelines. Even the Global Fund, which finances many national programs, does not consider the difference in quality of the products. In principle, Global Fund tender guidelines state that all nets recommended by WHO as Long Lasting Insecticidal Nets (LLIN) are practically identical in performance and durability – at least in the context of the procurement decision. A major international planning model made by Milliner from USDA takes the difference in net durability into account by assuming polyester has a durability of 3 years and that polyethylene net has a durability of 4 years. These assumptions are however not founded on well-documented data. The WHO studies of Permanet showed that in 2 out of 5 countries Permanet did not last 3 years [6]. The underlying data did not even include nets discarded by people, but only those that could be found at the time of collecting the nets years after their distribution. A study of Kilian [8] showed that when nets become deteriorated to a level where they lose effect, people tend to discard them. An improved study is now being carried out by USA Center for Disease Control (CDC) testing all long lasting insecticidal mosquito nets (LN) recommended by WHO in 2008 in a way that all nets can be traced and representative samples taken from the lots distributed. Several older studies do show that polyester nets are not very durable [9].

A field study with thousands of nets was carried out by the NGO Mentor in refugee camps. In these probably very harsh environments for nets, polyester nets lasted less than polyethylene nets, but none were very good after just one year use (R. Allen, poster in ASTMH, Nov 2009).

Therefore, including the older knowledge on polyester nets for dipping, a conservative estimate is that polyester nets can last physically about 2.5 years and polyethylene nets around 4 years. It should be noted that solid field data only exist for Olyset net, but laboratory strength measurements put Netprotect on par with Olyset. The durability of Duranet might be higher since it combines a heavy yarn and a tight mesh, but it is not known how durability is linked to yarn diameter, net bursting strength, net tensile strength and polymer. It should be noticed that in 2009, the WHO Pesticide Evaluation Scheme (WHOPES) evaluated a 5 year claim for durability of Olyset and discarded this, partly because the data provided did not take into account nets not found [6]. Interestingly, WHOPES found the same problem in the evaluation of Permanet 2 durability for 3 years, but the same consequence was not taken in the two cases [6].

## Long Lasting Insecticidal Effect

The aspects of durability of the insecticide treatments are more complex and not so easy to measure. The WHO test procedure describes sampling from bednets as one sample from the roof and 4 from the sides following a diagonal from top to bottom. All measurements on single bednets show that after some use insecticide concentration is highest on the roof and declining to the sides. This may be explained by people handling the sides of the nets daily either when rolling the net up in the morning and touching them while hanging. This real-life scenario is quite different from the WHO test model, in which nets are washed with few days intervals without any use, then hung in test houses and compared for effect. In this case, the insecticide distribution will be expected to be homogenous as loss will occur only from the washing process.

Is the heterogeneous distribution of insecticide important? A few studies on mosquito behavior in houses with eve openings show that in these houses, mosquitoes will enter by the eves and start searching from the top of the net for holes to enter. The top of the bednet has the fewest holes from tearing and highest insecticide concentration. A recent study presented at the MIM conference in Nairobi 2009 showed that even for nets only treated at the top or on the sides, as long as the nets were intact, the effect would be the same. This indicates that mosquitoes will search all over the nets for an entry. However, most investigations show that bednets become holed in the first year of use. Especially so for new users that are not accustomed to net usage and to the fragility of nets.

A simple way to see if a net is still killing mosquitoes is to attach a cone to the net and introduce mosquitoes into the cavity of the cone, so they can get in contact with the net. In this WHO standard test, mosquitoes are exposed to the nets for 3 min. This is a far cry from the reality described above where they search all over the net until picking up a lethal dosage. To compensate for this lack of reality of the standard test, WHO recommends in addition a so called tunnel test, if the net failed in the 3 min exposure. This is a glass tunnel with a net sample separating the tunnel at the middle. E.g., a guinea pig is placed on one side of the nets and the mosquitoes released into the tunnel on the other side. Small circular holes are cut into the net allowing mosquitoes to pass through by chance or by searching in order to get to bite the guinea pig. Test time, and thereby potential exposure time, is over 16 hours. So it is of little surprise that many nets that fail in the 3 min cone test will make it in the 16 hr tunnel test. In 2007 [6], WHO reported a study that compared the two test methods when testing nets with Permethrin (very contact repellent) to nets treated with deltamehtrin (less so). The study showed that results of cone test and tunnel test could only be interpreted when considering the pyrethroids had different effect. It is expected that the tunnel test better reflect real life than the cone test. It would therefore have been fair to conclude that the cone test has little predictive value, and one may wonder why the cone test is not changed so that it better reflect real life also. Perhaps something simple as increasing exposure time would help even if it would not solve all problems.

An apparently simpler way to solve these problems would be to use chemical analysis. However, depending on the insecticide treatment type, e.g., coated *versus* incorporated, a specific insecticide dosage may be effective or not. This may be caused by differences in availability of the insecticide even if the overall amount is the same. The only thing one can conclude with certainty is that if there is next to no insecticide left there will also be next to no effect.

## Net Distribution and Use

The advantage of the LN is that they are relatively easy to distribute, at least in principle, though the logistical organization is not a small task. Much effort has gone into making this process smoother and cheaper, e.g., by combining with vaccination campaigns for large-scale distribution and antennal clinics and voucher-based sales for "catch up". This has – at least on paper – brought the coverage up to near 80 % of the primary targets, small children and pregnant women, in several countries. For the extended target of all vulnerable, exposed people, coverage is also catching up if at a slower pace.

However, as many studies have shown [10, 11], a distributed net is not the same as a net in use and even less a correctly used net. Nets may be lost from final point of distribution to the household, may end up on a shelf in the house, be resold or simply hung incorrectly.

One may wonder why an insecticidal net as a proven tool against malaria is not used, but there are many and good reasons. A major cause of under-usage found in several studies is that a bednet is not really practical in a small house [10, 11]. Houses are used for various purposes as food preparation and storage of things during day time and nets have to be packed away. It takes time to put them up again. Further, kids may sleep on a carpet on the floor, and strings for hanging bednets in the middle of the room are too short and attaching points may not be easily reached. Bednet standard models need some rethinking to increase the use rate. Another problem is air movement. The mesh holes on multi-filament yarns become filled with fine filaments during use (washing with rubbing), which further hinders air passage. People often reject them when the nuisance problems of mosquitoes are reduced and the bednet become a greater nuisance than help. One may think that all this weigh little against the problem of getting malaria. But this observation ignores that for many adults in holo-endemic areas malaria is not a very dangerous disease since they have some level of immunity. People's priority is to sleep well, and when the bed net helps in that by keeping nuisance or malaria mosquitoes away, they are used. When these are few, people conclude that the trouble in using nets make them not worth the effort.

## Insecticide Resistance

Insecticide resistance is measured on locally caught mosquitoes using various methods. Simple bioassays measure if mosquitoes exposed to the insecticide of a certain dosage are killed. If there are no survivors in such a test, the local mosquitoes are considered susceptible. The more survivors found after an hour exposure, the more resistance there is in the mosquito population to that insecticide. These methods are therefore very well suited to show if resistance is present at a level that may be a problem. However, once this detection level has been reached, action has to be taken quite swiftly to find other ways of controlling the pest. Modern molecular biology tools and biochemical methods can detect resistance genes and their expression when these are rare and there is more time to react. They do not tell if the resistance found will develop into a problem, but they do provide an early warning.

For malaria mosquitoes in Africa, resistance mapping is overlapping with entomologist mapping. Several countries in West and East Africa have experienced laboratories that follow resistance closely, but larger parts of central Africa do not. The geography of resistance patterns is therefore not exact. Existing data shows that pyrethroid resistance is now appearing in several West African countries and spreading rapidly [12].

Insecticides used on bednets so far all belong to one group of insecticides, pyrethroids. Technical names of these insecticides are deltamethrin, alfacypermethrin and permethrin. In the same group one can also find lamdacyhalothrin, bifenthrin and cypermethrin, which have so far only been used for wall spraying (IRS). DDT works on the same receptor in the nervous system of insects as do the pyrethroids and resistance to pyrethroids by modification of this receptor therefore also provide resistance to DDT. These insecticides are not limited to vector control, but are also used in agriculture. Research has shown that the most likely reason for pyrethroid resistance developed especially in West Africa was the use in agriculture, but with the intense vector control campaigns now in play, this is likely to change and spread.

Several discussion forums have concentrated on ways of retarding or at least not to contribute to this resistance development. It seems logic what to do, but no clear policy has so far been formulated nor applied.

The important malaria vectors in Africa, *Anopheles gambiae*, *Anopheles arabiensis* and *Anopheles funestus,* all like to rest near or inside houses (both sexes), and bite indoor although *An arabiensis* will also willingly bite outdoor and feed on cattle. Spraying houses indoor will therefore generally expose males as females to the pesticides. Whereas for bednets, only females bite for blood and therefore only females get in contact with the insecticides. Therefore, bednets are not likely to provide such a high selection pressure as house spraying or similar tools (e.g., lining walls with insecticide treated textiles). Pyrethroids have some contact repellent effect and are fast acting, which make them very suitable for bednets. It is preferred that the mosquito does not rest on the net and try to bite trough the mesh (or find a hole and fly in). No other insecticides, except DDT, have this combination of properties that provide for personal protection. It is therefore sensible to preserve these for bednet use [7]. When the same product is applied to wall spraying or on textiles hung on the wall, resistance to both type of use is quickly developed with biggest damage for the bednets. Many other types of insecticides can be used on the walls since here we do not need a repellent effect nor the instant effect. Actually, it would be better if these were not repellent, since we want the insects to sit on the surface and pick up a lethal dosage. This knowledge of proper choice of insecticide for specific uses is so old that it was policy for resistance management in house fly control in Denmark back in 1974 [13]. Following the logic above, the Danish Ministry of Agriculture made a voluntary agreement with the pesticide industry not to launch products with pyrethroids for wall spraying in animal units in Denmark against houseflies. No such agreement was made in neighboring Germany. In 1978, the Danish Pest Infestation Laboratory sent me to the border area of Germany and Denmark to prove that their policy was correct. We sampled from a number of farms 20 km north and south of the border, and flies south of the border were all resistant to pyrethroids and the farmers could not use e.g. aerosols to make peace in the pens, pig houses and kitchen. In Denmark, however, resistance was very moderate and these tools were still effective. In general, the recommended methods for the farmers was to combine cleaning up, use of larvicides, baits with fly stomach poisons and aerosol bombs occasionally, the insecticides belonging to different groups. To-day, this is called Integrated Vector Control, but the principles for such approaches are not new and based on common sense. In India, such practice has been in use for years in the fight against malaria [14].

There is an old proverb that says those that do not learn from history are doomed to repeat the errors. We should not allow that in an area where it is a question of lives and health. There should be a clear policy advising not to use pyrethroids for wall spraying or in wall hanging textiles! If WHO has no authority to prohibit that, the pesticide industry should make it their policy as they did in Denmark 30 years ago. Most of these esteemed companies can support this decision by looking to their codes of conduct. If others fail, African ministries of health should take the lead to ensure a future with a good choice of tools for vector control!

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