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Culminating anti-malaria efforts at long lasting insecticidal net?



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KEYWORDS

LLIN;
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Summary

Background: Long-lasting insecticidal nets (LLINs) are a primary method in malaria control efforts. However, a decline in the biological efficacy and physical integrity over a period of comparatively lesser time than claimed, waning of naturally acquired immunity among regular users and misuse of LLINs are serious concerns.

Search and selection of literature: The literature for the current review was searched in PubMed, SCOPUS Database and Google using combined search strings of related key-words. Literature with sufficient data and information on the current subject was selected to reach a valid conclusion.

Findings: The World Health Organization (WHO) has emphasized that LLINs should be considered a public good for people inhabiting malaria endemic settings. LLINs exhibited a cumulative effect on the vector density and may force anthropophilic mosquito vectors to find alternative animal hosts for blood meal. However, the physical integrity and biological activity of LLINs declines faster than the anticipated time due to different operational conditions and the spread of insecticide resistance. LLINs have been successful in reducing malaria incidences by either reducing or not allowing human exposure to the vector mosquitoes, but at the same time, LLINs debilitate the natural protective immunity against malaria parasite. Misuse of LLINs for deviant purposes is common and is a serious environmental concern, as people believe that traditional methods of prevention against malaria that have enabled them to survive through a long time are effective and sufficient. Moreover, people are often ill-informed regarding the toxic effects of LLINs.

Conclusions: Specific criteria for determining the serviceable life and guidelines on the safe washing and disposal of LLINs need to be developed, kept well-informed and closely monitored. Malaria case management, environment management and

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community awareness to reduce the misuse of LLINs are crucial. Focused research on developing effective anti-malarial drugs, vaccines and new insecticides to reduce resistance is imperative to tackle malaria in the future.

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Introduction

Even after tremendous control efforts, malaria still remains a major cause of mortality in many Afro-Asian countries and carries a significant economic burden in the nations where it is endemic [1]. The malaria parasite *Plasmodium* has separate development stages in the human host and *Anopheles* mosquito. Malaria was once spread throughout most of the world; however, due to changes in the house designs, clearing of the breeding sites and the use of DDT after the Second World War, malaria was extinguished from the majority of northern countries. The concerted efforts to control malaria in endemic countries and step toward complete elimination in comparatively less endemic countries largely hinges on the latest effective tools available for prevention and treatment [2]. Malaria vector intervention through the use of long lasting insecticidal nets (LLINs) is considered a primary control method, and it is emphasized that LLINs should be considered a public good for people inhabiting malaria endemic settings.

The use of LLINs provides a physical barrier that reduces human-mosquito contact; furthermore, the insecticidal and repellent activity of the insecticide incorporated into the LLIN fiber protects the users as well as non-users by providing community protection through spatial effects [3]. LLINs used at the community-wide level can exhibit cumulative effects on vector density, survival and

longevity over a large area and may force *Anopheles* mosquitoes to find alternative animal hosts and ultimately reduce human malaria transmission [4]. Many studies across the world have revealed that LLINs were able to reduce the malaria burden and significantly reduce the uncomplicated malarial episodes in areas of both stable and unstable malaria transmission [3,5–8].

The introduction of insecticide treated bed-nets (ITNs), which were developed during the 1980s to prevent malaria in the Roll Back Malaria (RBM) program, proved highly effective in reducing malaria-related morbidity and mortality. The effectiveness of ITNs in reducing malaria was demonstrated for nets and cloths dipped in the insecticide solutions [6,9–11]. However, ITNs did not prove to be practical in the field because getting the net properly re-impregnated after 6–12 months was difficult. Further, the availability of insecticides when needed and the cost of the insecticides emerged as critical issues; the retreatment rates were reduced exorbitantly when people had to pay for the insecticides [12–15]. The LLINs were developed as a response to various problems associated with ITNs, and had several advantages over the latter. These were ready-to-use pyrethroid-treated nets that resisted washings and did not require re-impregnation for up to several years. Recent studies have suggested that the effective life of LLINs varied from two to seven years under different conditions [16–18].

While community wide use of LLINs has been identified as one of the most powerful tools in malaria prevention in recent years, there are some serious issues associated with the long-term use of LLINs. The development of resistance in mosquitoes against pyrethroids, the decline in net functionality over a period of comparatively lesser time than claimed and the waning of the naturally acquired immunity of regular users raises serious concerns that are debatable. We examined crucial outcomes of LLIN use and have attempted to evaluate them in respect to the desired success with an understanding that this information may be required to use LLIN optimally for malaria control efforts.

Search and selection of literature

The literature of PubMed, SCOPUS Database and Google were searched using a combined search string of key words including: ITN, LLIN, mosquito bednets, insecticide, insecticide-treated bednets, use of LLINs and ITNs, wash resistance of LLINs, repellent activity of bednets, willingness to pay for bednets, impregnation of bednets, re-impregnation of bednets, knockdown activity of LLINs, insecticide resistance in mosquitoes, pyrethroid resistance, immunity to malaria, mosquito bites and immunity, malaria reduction using LLINs, cost of LLIN and ITNs, distribution and use of LLINs and ITNs, misuse of nets, ownership of nets, motivation for using LLINs, meaningful coverage of bednets and effective life of bednets. Additional information on the subject was collected from the library of Defense Research Laboratory, Tezpur and recent blogs on Research Gate and Wikipedia. In addition, the issues raised currently were also discussed with the researchers and health personnel engaged in malaria research and control programs.

Many research papers were collected using the selected key words and library searches. In many cases of the literature search, the data and document retrieved were useful and contributed to at least one aspect addressed in the present study. The literature was considered if sufficient data and information were provided to come to a valid conclusion. Literatures published in non-indexed journals were not included in the review.

An operational description of insecticides used in LLINs

The use of LLINs in malaria endemic areas, in general, is based on operational requirements, epidemiological conditions and protection expected in

the control programs. The effective protection is a function of many factors including vector density, feeding preferences and the presence of insecticide resistance among potential malaria vectors [19]. Among the insecticide formulations approved by the World Health Organization Pesticide Scheme (WHOPES), permethrin, deltamethrin and alpha-cypermethrin were used as active ingredients in the LLINs. Currently four LLINs namely, Interceptor®, Olyset®, PermaNet 2.0® and Yorkool LN®, have been fully recommended for use, while additional nine LLINs have interim recommendations as they are in the evaluation stage. Further, long-lasting insecticide treatment kits specifically designed to transform untreated nets into LLINs by simple dipping are also in developmental process, which once approved would provide substantial options to treat millions of untreated mosquito nets currently in use in endemic counties [20]. Each insecticide has a distinct spectrum of insecticidal outcomes on mosquitoes, which imply that LLINs based on different insecticides may have different effects on mosquito vectors. Previous studies have suggested that LLINs elicited very low level of deterrence against susceptible mosquito vectors and were effective because they did not allow mosquitos to feed on the user [19,21–24].

The physical and biological integrity of LLINs

Recent studies have suggested that the use of LLINs reduces malaria-related morbidity by 50% and mortality by 20% [25,26]. Due to the substantial reduction of the malaria burden in numerous endemic setting worldwide by the use LLINs, LLINs have been strongly recommended for large scale deployment in countries that have a high burden of malaria and have yet to shift to LLINs. Several LLINs have been recommended by the WHO, and their biological and chemical integrity data have been comprehensively reviewed. Although LLINs have fixed key specifications, they may vary depending on the area of use. Some LLIN manufacturers develop LLINs with thick fibers that could be particularly useful in rural areas where ordinary LLINs with a thickness of approximately 100 denier might not last for the desired period [18,27]. The physical strength of LLINs has been found to increase the attractiveness and acceptability in rural settings. Studies conducted in Tanzania and Senegal have presented a very encouraging picture about the integrity and efficacy of the permethrin based LLINs [18]. These findings suggest that the LLINs were in

good physical condition after seven years of regular use under operation conditions and were equally effective in protecting the users from mosquito bites. The LLINs were able to produce a high level of knockdown effect against the known malaria mosquitoes. The insecticide content of the LLINs was found to be persistent with approximately 40% of the insecticide still present in the LLINs at the last measured time point.

However, a recent investigation from Ethiopia revealed that after approximately six months of regular use in the field, the majority of LLINs were deteriorated, of which approximately 68% had holes [28]. There were numerous holes and their distribution was highly skewed, and the LLINs were found to be heavily damaged in certain places. Holes were observed on all five sides of the LLINs including the top, indicating that the damage did not occur due to mishandling but rather from natural use. In Uganda, Kilian et al. [29] observed that most of the LLINs were significantly damaged within one year and were not fit for use over time. Further, in Tanzania it was observed that LLINs started to show signs of damage after two to three years of regular use [30]. In Chad, a recent study [31] involving field evaluation of two WHO recommended LLINs revealed that 25% LLINs were not fit for use and or repair, while 44.5% required major repairs after one year of use. The damaged and torn LLINs have been shown to increase human-mosquito contact; despite the use of the LLINs, the user received up to five bites per night [3,32]. Gnanguenon et al. [33] found that LLIN loss occurred more rapidly than predicted by the 'three-year serviceable life' assumption included in the standards for LLINs as a malaria prevention. The study further suggests that the assumption of three years serviceable life of the LLINs was grossly overestimated and created a situation that could contribute to malaria rebound well before the replacement of the LLINs.

Currently, the replacement of LLINs is based on the assumption that they have a useful life of three to five years, but the critical question about the real operational life of LLINs remains unanswered. A LLIN will not allow mosquitoes to bite the user if its mesh is intact, but if the mesh is not intact, the mosquitoes will attack the user. Most of the studies involving field evaluations of LLINs began after at least one year of distribution because the LLINs are supposed to last for many years. However, meaningful data on the exact effective age of LLINs considering their deterioration rate in the field setting is important. Data comparing the performance of LLINs in different countries and sometimes between different areas may be useful to determine when LLINs should be

classified as un-serviceable and require repair or replacement.

The development and spread of pyrethroid resistance

The rapid selection and spread of operationally significant pyrethroid insecticide resistance to new geographical areas has threatened malaria control using LLINs in areas where pyrethroids are used for protection against vector mosquitoes. The decreased insecticide sensitivity among the mosquitoes could make the LLINs ineffective by allowing the resistant mosquitoes to enter the nets through holes. Yewhalaw et al. [3] established that repeated exposure to LLINs has resulted in low knockdown and mortality in *Anopheles* due to metabolic resistance and knock down resistance mutation. Further, the study observed reduced efficacy of WHO recommended LLINs against four malaria vectors populations in Ethiopia. This study provided compelling information that pyrethroid resistance was developed among the *Anopheles* populations and may be a serious concern for obtaining sustained efficacy of pyrethroid-based LLINs. The resistant mosquitoes are capable of standing the excito-repellency effect of the LLINs and penetrate through the LLINs to take blood meal from the human sleeping under the net [33]. Failure to take a blood meal reduces the mosquito's longevity, but the resistant mosquitoes are able to feed and are likely to have increased longevity compared to the susceptible mosquitoes. Studies have revealed that in areas that report high levels of pyrethroid resistance, anopheline vectors are routinely recorded inside the LLINs [34], which were attributed to the reduced susceptibility of these vector mosquitoes to pyrethroid. The mortality in the adult mosquitoes raised from the resting mosquitoes inside the LLINs was approximately 35%. A recent investigation in Zanzibar suggested that insecticidal activity decreased after two years of use, resulting in only a 45–60% mortality rate among the mosquitoes [35]. Moreover, in Vanuatu, although the nets were claimed to last for five years, the efficacy declined after three years of use under programmatic conditions. The insecticidal efficacy obtained for three-year-old nets was 80%, which indicated an increased risk of getting infective mosquito bites and also increased anopheline exposure to sub-lethal dosages of insecticide [36].

Pyrethroid insecticide resistance among known anopheline vectors may have increased in response to agricultural activity or increased selection

pressure owing to the use of LLINs, but regardless of the source, it has largely undermined control programs. Development of resistance has been reported in many areas, but there is surprisingly little or no information about the association of insecticide resistance and the biological activity of LLINs in many endemic areas. WHO recommendations for the use of LLINs have been based on the evaluation of bio-efficacy data from only three geographically distinct malaria endemic settings, however conducting resistance and bio-efficacy studies using local mosquito populations could be useful for taking a decision on recommending LLINs in an area of interest.

Actively acquired malaria immunity

Humans with no previous exposure to malaria develop febrile illness when first infected with the malaria parasite, which may become severe and fatal in some cases. Young children are particularly susceptible; however, after some time with exposure to the malaria parasite they develop protection from severe illness, although complete sterile immunity is most likely not achieved. The parasite rapidly moves to the liver in the human and undergoes division in an asymptomatic stage before finally entering the blood. Immunity to malaria in endemic areas is prevalent and is demonstrated in the lower parasitization of blood cells and rapid control of successive malaria infections, which lowers parasite density and does not result in clinical illness [37]. Studies have suggested that immunity to malaria is developed slowly and is always incomplete; however, immunity to malaria-related deaths is acquired quickly and may be important even after a single episode of malaria [38]. Therefore, due to the rapid development of malaria immunity that occurs after mosquito bites, the use of interventions that either do not allow or reduce human exposure to infection require critical consideration. Many studies have suggested that infections are essential in providing comprehensive protection against malaria, and have also determined the minimum number of infections required to considerably reduce the risk of severe malaria [38].

The long-term use of LLINs at 100% coverage would provide sustainable protection against mosquitoes, but would also debilitate the natural protective immunity against the malaria parasite. The naturally acquired immunity; however, does not incite long protection, but renders individuals to be more susceptible to malaria infection and protects millions of people routinely. The repeated,

though less severe, malaria infections develop natural immunity in people, making them less likely to succumb to the immunopathology associated with malaria when they move into malarious areas. The malaria parasites multiply to extremely high densities in a weakened immune system and might contain a larger number of mutants, which could unexpectedly increase the chances of greater virulence potential. Anything which leads to a weakened immune system will lead to a higher *Plasmodium* load in the infected individual. Many studies have argued that malaria interventions could interrupt the accumulation of sufficient antigens in the humans and perhaps may increase the susceptibility of children to more severe malaria [39,40]. These studies further suggest that interventions that allow children to pass up to a certain age to develop sufficient immunity could decrease the risk of severe malaria and prevent a rebound in malaria cases [39,41,42].

Currently, movement of non-immune people into the malaria endemic countries occurs under many circumstances, making them vulnerable for developing severe illness due to malaria. In the present review, we do not suggest that intervention measures, including antimalarial chemoprophylaxis and the use of LLINs, which largely protect against malaria infection, be reduced, but instead emphasize that their uninterrupted use might lead to compromised malaria-related acquired immunity.

The problem of LLINs misuse

Since the inclusion of LLINs in anti-malaria programs in many endemic countries worldwide, LLINs are distributed free of cost by government agencies and many Non Government Organizations (NGOs). Because the problem of insecticide resistance has been found to be associated with the low dose of insecticide in LLINs and sometimes due to selection pressure, it is obvious that LLINs should be used for personal protection against mosquitoes only. Reports from various regions have revealed that LLINs were used for deviant reasons, including trapping fishes in the rivers, as well as to protect and store food material (<http://ammren.org/content/mosquito-bed-net-abuse-zimbabwe>). People believe that their traditional malaria prevention methods that have enabled them to survive over time are sufficient. Although users are given knowledge and awareness about the LLINs, the rate of misuse is still considerably high. Many investigations have studied the misuse of LLINs and found that a considerable

portion of people do not adhere to the recommended LLIN usage practices [43–45]. Another study revealed that a considerably large number of bed nets were used for fishing and drying fish in a study area adjacent to Lake Victoria [46,48].

Washing and safe disposal of LLINs

Although most of the synthetic pyrethroids have been proven to be relatively safe, they may pose a threat to the environment if not handled properly. Many times, the left over waste water after washing the nets is not properly disposed of and sometimes re-enters the water source. Insecticide in water sources may harm aquatic life and other animals that use polluted water for their basic water requirements. Not much has been apprised about the recycling or disposal of the LLINs after their useful life is over.

While much emphasis is given on the distribution and use of LLINs, the issue of community education about the safe handling of these nets remains largely unattended and ignored. People remain ill-informed about the fact that LLINs have insecticides that are very toxic and could be dangerous if mixed into the water sources. Many recent studies have suggested that the LLINs were used for fishing in water bodies and therefore polluting the water [46–48]. Studies further suggest that malaria transmission is high near such areas. These water bodies have many mosquito breeding habitats and it is obvious that the insecticide from the LLINs might enter the breeding water [46,49]. Furthermore, regular exposure of mosquito larvae to the pyrethroid may increase the resistance level of malaria vectors, and LLINs might not produce the expected malaria control results. Although the environmental risk associated with the insecticide treated materials has been calculated to be non-significant in relation to the benefits, the overall exposure risk threshold remains arguable due to operational uncertainties and unknown exposure levels [50].

Conclusion and recommendations

Although LLINs have been able to reduce the malaria burden in recent years, the risk of insecticide resistance development in the *Anopheles* vectors due to selection is a serious challenge that demands identification of new and non-pyrethroid based insecticides for treating LLINs and other anti-mosquito materials. Insecticide resistance can

be tackled by implementing resistance monitoring within the vector control management to guide insecticide use. Considering various aspects associated with the integrity of LLINs, specific criteria for determining the serviceable life and guidelines on safe washing and disposal of LLINs need to be developed, well informed and closely monitored. Active and voluntary participation of all stakeholders in malaria case management, environment management, community awareness, strengthened educational and communications to reduce the misuse of LLINs is indispensable. In addition to focusing research on developing effective anti-malarial drugs for treatment, vaccines for immunity against malaria and exploring alternative and new insecticides to reduce resistance, wholehearted partnerships between control agencies and the public at risk are essential in addressing malaria and other mosquito-borne diseases in the future.

Conflict of interest

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