Chapter

Finding Novel Strategies to Overcome the Impact of Malaria Vector Resistance in Limited-Resources Settings. The Case of Cameroon as a Basis for Reflection

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Abstract

Malaria remains one of the most important and deadliest diseases in many countries in Africa, in the Americas, in South-East Asia, in the Eastern Mediterranean and in the Western Pacific regions, with high morbidity and mortality, despite important successes for the control of this disease borne by the vector *Anopheles* mosquitoes. Malaria elimination relies on different strategies including early diagnosis, improved drug therapies and better health infrastructure, and mainly the use of long-lasting insecticidal nets (LLINs) and indoor residual sprayings (IRS) of insecticide. In Cameroon, a country composed of several ethnic groups, malaria transmission is endemic in some regions, while it is seasonal in others; children and pregnant women are most vulnerable. Progress has been made towards malaria control, considering these specificities, and led to a reduction in both morbidity and mortality, but these accomplishments are under threat, mainly due to the development of resistance to insecticides among mosquitoes, targeting the 4 commonly used insecticide classes. To continue our route towards malaria control and elimination, it is urgent to have more knowledge about resistance mechanisms, in the objective of elaborating new strategies with the involvement of the community; these strategies should take into consideration socio-ecological factors such as the young age of the population, low literacy rate especially among women, population's beliefs, traditions, and customs. Forest ecosystems with abundant rains, humidity and hot temperature, lower access to water for populations living in rural areas, and poverty level are other factors to consider when elaborating malaria control approaches.

Keywords: Malaria, Anopheles, vector resistance, sociology, novel strategies, insecticides, community, research, social change

1. Introduction

Malaria is one of the most important and deadliest diseases in many countries in Africa, in the Americas, in South-East Asia, in the Eastern Mediterranean and

in the Western Pacific regions. Malaria related morbidity and mortality remain high, despite important successes for the control of this disease borne by the vector *Anopheles* mosquitoes. In 2019, 229 million people suffered from malaria, with around 409,000 deaths, mainly in sub-Saharan Africa [1].

Important efforts have been made throughout the world to eliminate malaria leading to significant reduction in malaria cases and mortality in Africa by 44% and 67% respectively for the period 2000–2019, thanks to different strategies including early diagnosis, improved drug therapies and better health infrastructure, and mainly the use of long-lasting insecticidal nets (LLINs) and indoor residual sprayings (IRS) of insecticide [1].

In Cameroon, progresses have been made towards malaria control, and the number of deaths has been reduced from 1 million in 2000 to less than 450.000 in 2017. In parallel, morbidity was reduced from 41–26% in 2018 [2]. However, these accomplishments are under threat, mainly due to development of resistance to insecticides among mosquitoes, and this resistance targets the 4 commonly used insecticide classes – pyrethroids, organochlorines, carbamates, and organophosphates [3, 4].

Cameroon's population is composed of several ethnic groups, living in different regions with important diversity. In some regions, malaria transmission is endemic, while it is seasonal in others [2]. Children and pregnant women are the most affected and therefore most vulnerable.

To prevent the development of resistance, it is urgent to have more insight into resistance mechanisms and factors, intending to elaborate innovative strategies and to continue our path towards malaria control and elimination.

For this article, we reviewed official statistics from known public health agencies (WHO, CDC, UNICEF, etc.) and from Cameroon National Malaria Control Program, the coordinating body in charge of defining and implementing malaria control strategies and interventions. We also read various studies conducted not only in Cameroon, but also in other parts of the world, that could serve as benchmark to design and/or adjust intervention strategies besides vector control using indoor residual spraying (IRS) and the use of impregnated bed nets (ITN) [5].

This article intends to assess antimalarial drug resistance as well as insecticide resistance, especially for the Anopheles species found in Cameroon, and to suggest other strategies such as the use of new insecticides, and other vector control interventions that should be population-based, using specific communication strategies, and advocating for policies to improve the health of a given population. [6, 7].

By performing within interprofessional teams, one will be able to assess the positive social change impact that will occur because of this type of intervention [8].

2. Overview of malaria control and sociodemographic description of Cameroon regions

2.1 Description and organization of National Malaria Control Program (NMCP)

Cameroon National Malaria Control Program (NMCP) is the coordinating body in charge of defining and implementing malaria control strategies and interventions. In 2002, the minister of Public Health signed a decision reorganizing malaria control in Cameroun, highlighting the priority role of NMCP [9].

At national level, management of NMCP is ensured by the National Committee Roll Back Malaria (CRBM) presided over by the minister of Public Health (MINSANTE). Vice-President is a medical personality named by the MINSANTE, and CRBM is composed of several members among them representatives from the

Presidency, Prime Ministry, Ministry of Public Health and almost all other ministries, along with representatives from private sector, charity organizations, Non-Governmental Organizations, Donors involved, and Development Partners.

The Central Technical Group of NMCP is the executive body of CRBM, led by a Permanent Secretary. It is composed of 6 sections: 1) Management, 2) Prevention, 3) Information/Communication/Social Mobilization & Partnership, 4) Training and Research, 5) Administration & Finances, 6) Surveillance, Monitoring & Evaluation. At regional level, there are Regional Units for malaria control, with Cost Accountant and Statistics cells [9].

NMCP has also an important number of Technical and Financial Partners (PTF) that are involved in research, communication, social mobilization, case management and prevention namely [2]. Therefore, to conduct any malaria-related project, given the high-level management involved in National malaria control in Cameroon, there is a need for approvals from Permanent Secretary of NMCP.

Cameroon National Malaria Control program (NMCP) vision is to have "an emerging Cameroon without malaria", and its mission is related to universal and equitable access to the most efficient interventions in terms of prevention and case management, in an affordable cost for the whole Cameroonian population, including the most vulnerable and the most in need [2].

NMCP guiding principles are health equity and human / gender promotion, community participation, optimal management of the health information and stratification of interventions, quality of care and services, good governance, decentralization, leadership, partnership, multi sectorial collaboration, and result-based management [2].

In order to reach the goal to have a malaria-free Cameroon, NCMP has defined 4 pillars and strategic axes among which training and research; several interventions are necessary and include prevention, using insecticide-treated nets and indoor residual spraying; case management; monitoring & evaluation, epidemiological surveillance and response, communication for development, training and operational research, among which entomologic studies including observing insecticide resistance management [2, 10, 11]. Other activities consist of elaboration of cartography on malaria transmission, and study on the evolution of antimalarial (drugs) resistance molecular markers [2, 12].

In its Strategic Plan, NMCP has also foreseen to elaborate mapping of partners intervening in research, and cartography of malaria transmission to detect areas with high resistance towards specific insecticides or antimalarial drugs. Other axes of research include the assessment of the therapeutic efficiency of antimalarial drugs. Finally, there is a plan to create review committees with partners and to have a platform where research results would be shared [2].

2.2 Sociological factors affecting the health of the population in Cameroon

According to demographic projections from the Ministry of Public health, Cameroon population is around 25.5 million inhabitants in 2019, with children under 5 years and pregnant women representing respectively 15% and 3.6%, and considered as the most vulnerable categories, though the whole population is at risk of developing malaria [2]. Social determinants of health include the young age of the population: median age is 17.7 years; average age is 22.1 years; people less than 15 years and under 25 years represent 43.6% and 64.2% respectively. Mortality is still high among children under 5 years, around 60‰ [13].

Other elements consist of low literacy rate especially among women, which is around 64.7%. Cameroon is composed of Christians, Muslims, and Animists with more than 250 ethnic groups having their specific and diverse traditions

and customs, all of them influencing their participation in health interventions. The Center region is concentrating more than 20% of the population, and is part of the south forest ecosystem, with abundant rains, humidity, and hot temperature, allowing the development of malaria vector. In addition, and according to regions, between 20% and 65% of the population is living below the poverty level. Households are directly financing health care, which is an important load especially for malaria that is increasing dramatically family expenses [2].

Finally, access to water is lower for populations living in rural areas compared to those living in cities; gender approach is not well considered, due to the low literacy rate among women, and their low presence at management position.

Beside official or conventional communication and social Medias, other means are available such as drama, role playing, with the involvement of community health workers [2].

3. Malaria resistance status: synthesis of literature review

Malaria elimination is based on several strategies among which the use of long-lasting insecticidal nets (LLINs) and indoor residual sprayings (IRS) of insecticide. However, a majority of mosquitoes' species vector of malaria and found in the African continent develop resistance towards the main insecticides used, thus hindering the efforts to control this disease.

While it is important to have an overview of the current resistance status, it is also crucial to understand resistance mechanisms to develop novel approaches.

A study aiming at investigating the relationship between malaria insecticide resistance and effectiveness of impregnated bed nets was conducted in five African countries that were using Pyrethroids as the main insecticide for bed nets or indoor residual spraying (IRS) [14]. During 4 years and 5 months between 2012 and 2016, 1.4 million follow up visits were carried out, and in each of the selected clusters, community health workers (CHWs) monitored 40.000 children and measured clinical malaria and prevalence of this infection; in parallel, 80.000 mosquitoes were tested for resistance using the WHO bioassay test.

The authors found that children using insecticidal bed nets had lower prevalence and malaria incidence, even though they were exposed to high malaria infection risk. To the contrary, they found no correlation between insecticide resistance and malaria incidence or prevalence, indicating that the use of long-lasting insecticidal nets remains important to reduce the risk of infection. However, with a limited protection provided by bed nets, there is a need for supplementary vector control tools to reduce malaria burden.

This study is somehow representative of the situation found in many African countries and could be used to support the necessity of alternative ways of controlling malaria and to support the usefulness of impregnated mosquito's nets.

Another study conducted had the objective of defining resistance and understanding resistance mechanisms, types, and impact of resistance along with resistance status in African malaria vectors [15].

While they reminded the causes of resistance and stated the limited number of studies related to the epidemiological impact of resistance on current malaria control activities, the authors highlighted the need for further research and prompt response to resistance management to avoid jeopardizing current interventions. Despite the alarming observation that resistance is reported to all four classes of insecticides, there are few initiatives such as The Innovative Vector Control Consortium (IVCC), a partnership to stimulate research related to better makings of insecticides [16].

Even though this review is quite old, it is still useful as the authors proposed the development of non-insecticidal methods to help reduce the dependence on pyrethroid insecticides and given the long process to have new chemicals for malaria control programs.

In an article presenting the evolution of insecticide resistance over the last 30 years in the main malaria vectors in Cameroon, other authors reviewed 33 scientific publications and found that resistance was widespread in the two main Anopheles species, and concerned mostly DDT, permethrin, deltamethrin and bendiocarb insecticides [17]. They also noticed the different mechanisms involved in resistance towards each of the insecticide.

The review is of interest since it provides an update of insecticide resistance status in malaria vector populations in Cameroon, while insisting on the necessity to implement additional interventions to reinforce malaria control strategies in the future.

Some researchers categorized insecticide resistance of 2 anopheles' species to assess its impact on malaria control in the main city of Democratic Republic of Congo (DRC) [18]. They collected mosquitoes and sent them to London with their eggs for analysis, which reveals high and multiple insecticide resistance patterns, along with a low efficacy of mosquito nets impregnated with conventional insecticides.

Although it was limited to the city capital of DRC, this study highlights the urgent need for actions to better manage the issue of insecticide resistance and could be useful for other countries with a similar resistance pattern. In this respect, malaria control programs would remain effective.

In another study, Riveron et al. [19] monitored the aggravation of resistance and assessed its impact on the usefulness of control methods based on insecticides in Mozambique. They collected indoor female Anopheles mosquitoes in a village of farmers where most families had impregnated bed nets, and where indoor residual spraying (IRS) with dichlorodiphenyltrichloroethane (DDT) was applied. The authors observed an important loss of effectiveness of impregnated bed nets, even those using the new insecticide piperonyl butoxide (PBO). They manage to determine the main mechanisms involved in this insecticide resistance.

Despite the fact that it was conducted in a village of the Southern part of Mozambique, this study is important as it reveals multiple resistance of malaria vectors to insecticides, associated or not with PBO; the consequences of this could be the abandon of PBO if immediate action are not taken, provided that PBO-based nets be further assessed.

Other authors tested the hypothesis that female-driven auto dissemination of insect growth regulators (IGRs) that are used to reduce population of some insect species could be also efficient to reduce Anopheles population [20]. They exposed female Anopheles to three substances namely novaluron, pyriproxyfen and triflumuron for 4 hours immediately after blood feeding, and observed that larval survivability and adult development were meaningfully reduced in habitats that were visited by novaluron treated adults; to the contrary, there was no statistical differences with pyriproxyfen or triflumuron, suggesting that novaluron was horizontally transferred from the adult mosquito to the larval habitat during oviposition.

The study suggested that autodissemination method with novaluron could be useful as a novel approach to manage Anopheles populations, with regards to the need for a method that is cost efficient, sustainable, and requires minimal human intervention. However, there is a need to perform more experiences in the field to ensure the reproducibility of such study.

In another article, the dynamics of deltamethrin resistance in Anopheles populations found in the North Cameroon was explored [21], and researchers collected mosquito larvae from 24 locations of three Health Districts between 2011 and 2015. The authors tested female mosquitoes for deltamethrin resistance and observed that

resistance was mostly found in urban settings compared with semi-urban and rural settings, and that there was a rapid increase and widespread deltamethrin resistance.

Even though the study was carried out in few areas, it is reproducible in other parts of the country and it highlights the urgent need for vector surveillance and insecticide resistance management strategies adapted to the context.

Meanwhile, the vulnerability of major malaria vectors towards insecticides used for IRS and bed nets in Tanzania was screened [22]. The authors collected mosquito larvae in 20 sites of Tanzania mainland in 2015 and determined resistance and distribution of *Anopheles gambiae* sub-species. Results showed that almost all sub-species presented resistance to the four main insecticides, reinforcing the need to implement resistance management strategies.

This is another study confirming the high level of insecticide resistance in an African country, showing the necessity of collaborative efforts to find rapid response to this worrying topic.

Finally, some authors compared the efficacy of non-pyrethroid insecticide-treated, durable wall lining (ITWL), long-lasting insecticidal nets (LLIN), and non-pyrethroid ITWL + LLIN [23]. This novel ITWL was developed to control vectors when fixed to the inner walls of houses, and this product is responsible for a low mortality among Anopheles species, despite high mortality in bioassays.

Results on mosquitoes mortality were below expectations, even though it was evaluated for only two months, but insecticide resistance and low efficacy are probably responsible for this situation, since the ceiling of the hut was left uncovered, allowing some mosquitoes to find refuge on this untreated surface.

This is a promising study even though there is a need for further experiences on the use of this new non-pyrethroid insecticide, comparable to a long-lasting indoor residual spraying, when fixed to the inner walls and ceiling of houses.

4. Success factors and prerequisites for malaria resistance management

4.1 Sustainability

In contexts where various resources are limited there is a need for sustainability plan that will include several components, starting with interventions that could have an important public health impact especially on morbidity and mortality rates among children. Political support and partnerships with many International Organizations and Public Health agencies should be ensured, to have a funding stability [24].

Besides NMCP, there are several institutions dealing with malaria in Cameroon, for instance the Coordination for the Fight Against Endemics in Central Africa (OCEAC), which coordinates research on epidemics and endemics in Central Africa, and where many researchers are working. Any study absolutely needs their support and complete appropriation, unless at risk of failing. Other partner's organizations include WHO, UNICEF, and some other United Nations Agencies, as well as Associations working on social mobilization and fundraising.

All these stakeholders will work in close collaboration and under the supervision of the Training & Research Unit of NMCP, and its Technical and Financial Partners (PTF) that are involved in research [2].

4.2 Partnerships

Funding or financial capacity are essential to conduct interventions in the field of malaria vector resistance, along with the collaboration of specialized and experienced staff to perform evaluation [25].

A combination of literature review and field work is required in order to verify resistance status and mechanisms in the defined regions of a given country, for instance Cameroon. Some studies have already been conducted in some African countries, and it is important that the situation be assessed precisely in the chosen region to ensure its adequacy and its specificity, having other studies serving as benchmark [5, 7]. In addition, the World Health Organization (WHO) has elaborated several guidelines and procedures related to insecticide resistance monitoring in malaria vector mosquitoes.

In order to propose novel strategies, referring to existing studies conducted in other places, and assessing their reproducibility and feasibility will be important.

4.3 Program evaluation

Insecticide resistance is an important issue that needs to be well understood and tackled in the best way. There is a need to understand its mechanisms and to have a broad picture of its status in the area where interventions are planned.

Therefore, it is crucial to evaluate if a project is conducted appropriately and if there are positive results to influence decision-making process [26]. Evaluation methods will include process evaluation, outcome evaluation and impact evaluation.

Process evaluation will assess how well insecticide resistance studies are working, and whether they are being implemented as designed; it will allow researchers to monitor their intervention and will serve for staff and program managers to apply corrective measures.

Outcome evaluation will assess effectiveness in identifying resistance mechanisms and proposing alternative interventions, and impact evaluation will provide evidence for decision-makers and donors on the need to develop alternative malaria control strategies, which necessitate funds and support.

Methods of evaluation should use a combination of interviews with key informants who are credible to gather more information, questionnaires, records, and documentation research. For impact evaluation, community dialog and surveys within target population could also be used [27–29].

4.4 Ethical considerations

Some ethical concerns such as handling of data and their confidentiality must be considered, as people from the community would be involved. In addition, when it comes to proposing alternative strategies, there are a number of other ethical issues related to malaria and vector research that need to be addressed such as environmental aspects and climate change, the use of products or chemicals and experimentation on vulnerable groups among others [30–32]. In some cases, humans are used as mosquito 'traps' to measure mosquito or malaria density; it will be essential to balance potential harms to a few individuals against benefits to the wider community [30].

As alternative ways of combatting malaria, the use of vaccines and genetically modified (GM) mosquitoes have been suggested. While vaccines provide some protection against severe malaria in children but not infants, the question of using placebo or other vaccine as control arm in other trials is raised. For the use GM mosquitoes, the ecological consequences are not well understood, and ethical issues relate to the balance between potential improvements in population health and possible environmental harms, since it would be difficult to control these mosquitoes once they have been released [30].

Further research on ethical issues related to malaria is needed, to inform ethics review processes linked to control interventions, and assist health workers, researchers, and policymakers in pursuing ethically sound malaria control efforts [30].

4.5 Evaluation process for new vector control products (WHO)

Before being used, any product for vector control needs to pass through a rigorous process put in place by the WHO and aiming at improving access to high-quality vector control and promoting the best use and management of vector control tools. Product with a WHO policy recommendation pass through a prequalification pathway while those without policy recommendation need to be first assessed on their public health value [33].

4.6 Use of randomized controlled trials and mathematical modeling

Financial and other constraints are likely to prevent the need to conduct necessary field trials to evaluate novel vector control tools; nevertheless, some authors proposed that new products within the same product category be evaluated through smaller scale experiments, especially where links between entomological and epidemiological indicators are well-known [34]. Other authors tested the utilization of mathematical modeling that may reduce the need for phase III studies in some instances but conclude that a better understanding is required to inform predications of impact [34].

5. Investigating novel strategies for 'limited-resources' contexts

There are new vector control tools and strategies that need an interdisciplinary approach to overcome malaria vector resistance that have been tested, from household-level vector control tools to biotechnological control of mosquitoes. Some examples include the use of attractive toxic sugar baits, eave tubes, nano-synthesized pesticides loaded with microbial and plant-borne compounds, biocontrol agents with little non-target effect, new adult repellents, oviposition deterrents, even acoustic larvicides. Their concrete application remains limited since most countries rely on IRS and LLINs [35]. In low-resources contexts, some authors have observed that simple changes in the built environment or housing could have great benefit. Further research is needed, and the combination of several strategies would have a better impact [35, 36].

In the future, other areas could be explored such as the development of targeted sugar baits, transgenic fungi that will be disseminated from bait stations, and even the potential role of volatile odor compounds, bioinsecticides and technologies for improving the incorporation of insecticides and repellents into clothing and other materials [34–36].

6. Conclusions

Despite a certain number of studies on malaria vector resistance, there is still a need for research on insecticide resistance, given the fact that vector control using these chemical products remains one of the most important strategies towards malaria elimination. This literature review provides elements to help us understanding the status of the resistance towards the four main classes of insecticides

and some of its mechanisms, but also to perceive the gap in addressing this kind of research, especially in countries with limited resources.

Novel strategies could involve the use of alternative chemicals, such as non-pyrethroid ones, and/or some methods like auto dissemination with novaluron that could be useful to manage Anopheles populations, with regards to the need for a method that is cost efficient, sustainable, and requires minimal human intervention. However, there is a need to perform more experiences in the field to ensure the reproducibility of such study.

We are confident that further projects and research would be implemented and would contribute to better address insecticide resistance by proposing alternative ways of controlling malaria and its vectors.

Conflict of interest

We declare no competing interests.

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