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Developing an Evidence-Based Decision Support System for Rational Insecticide Choice in the Control of African Malaria Vectors

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J. Med. Entomol. 43(4): 663–668 (2006)

ABSTRACT The emergence of *Anopheles* species resistant to insecticides widely used in vector control has the potential to impact directly on the control of malaria. This may have a particularly dramatic effect in Africa, where pyrethroids impregnated onto bed-nets are the dominant insecticides used for vector control. Because the same insecticides are used for crop pests, the extensive use and misuse of insecticides for agriculture has contributed to the resistance problem in some vectors. The potential for resistance to develop in African vectors has been apparent since the 1950s, but the scale of the problem has been poorly documented. A geographical information system-based decision support system for malaria control has recently been established in Africa and used operationally in Mozambique. The system incorporates climate data and disease transmission rates, but to date it has not incorporated spatial or temporal data on vector abundance or insecticide resistance. As a first step in incorporating this information, available published data on insecticide resistance in Africa has now been collated and incorporated into this decision support system. Data also are incorporated onto the openly available Mapping Malaria Risk in Africa (MARA) Web site (http://www.mara.org.za). New data, from a range of vector population-monitoring initiatives, can now be incorporated into this open access database to allow a spatial understanding of resistance distribution and its potential impact on disease transmission to benefit vector control programs.

KEY WORDS decision support, insecticide resistance, malaria

Malaria control is currently dependent on decreasing the number of infective bites from the vector to reduce transmission, either by use of insecticide-treated bed-nets (ITNs) or indoor residual spraying (IRS) of insecticides, coupled with prompt treatment of malaria cases by effective antimalarial drugs. Ninety percent of all malaria mortalities occur in sub-Saharan Africa (WHO 1999), where most countries have had no systematic malaria vector control operations in place. Even the failed WHO malaria eradication campaign of 1955–1969 only included Ethiopia, South Africa, and southern Rhodesia (Zimbabwe) (Trigg and Kondrachine 1998). In 2000, the African heads of state signed the Abuja declaration, which launched the WHO-led Roll Back Malaria (RBM) initiative, with the stated aim of reducing malaria mortalities by 50% by 2010. The RBM initiative was complemented by the launch of the Global Fund for Aids, Tuberculosis, and Malaria (GFTAM) in 2001, developed as an internationally supported funding mechanism to allow countries to establish better control systems for these three major diseases. The GFTAM has increased the funding available for communities to improve malaria control efforts and stimulated a rapid increase in operational vector control programs in Africa.

The reinvigoration of multiple vector control programs in many African countries with GFTAM funding is hampered by the lack of trained personnel, the perception that large-scale national vertical malaria control operations are unsustainable, and the inability of public health infrastructures, in most disease endemic countries, to comprehensively deliver either IRS or ITN programs. These problems are compounded by the dual issues of drug resistance in the parasites and insecticide resistance in the vectors, which if not monitored directly are only detected once operationally significant increases in disease transmission and childhood mortality occur.

The resistance phenomena in microbes, parasites, and insects to agents used to control them has many parallels. This resistance threatens the long-term ability of humans to control the diseases conferred by these agents, particularly as resistance is evolving at a faster pace than new antibiotics, drugs, and insecticides are being developed and marketed. Hence, the historical response of waiting until an epidemiologically significant endpoint for disease, to assess whether a drug or insecticide has failed, before moving on to a second-line treatment is no longer sustainable, and resistance management is essential if we are to conserve these scarce public health resources.

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With antimalarial drugs, there is an increased awareness of chloroquine and sulfadoxamine pyremethamine drug resistance in the malaria parasite *Plasmodium falciparum* (Plowe 2003, Anderson and Roper 2005). This has led to recent coordinated calls for a change in the first line treatment regimes, moving from single-drug treatment to antimalarial combination therapy (ACT) to provide effective treatment and halt the inexorable spread of resistance to the small number of antimalaria drugs available. In contrast, the documentation and understanding of insecticide resistance in African malaria vectors is less well developed but no less of a threat to sustainable malaria control. This is particularly so when malaria vector control is primarily based on ITNs, because at present, only one class of insecticides, the pyrethroids, are recommended by World Health Organization (WHO) for net treatment.

Here, we review the published locations on insecticide resistance and the documentation of the underlying resistance mechanisms and report on the incorporation of this into a decision support system (DSS) linked with a geographical information system (GIS).

Materials and Methods

Insecticide resistance data that should inform effective vector control policy has never been collected in a systematic manner. Published data have now been collated and a database established to ensure that this information is available to the malaria control community. A comprehensive literature search for *Anopheles* and insecticide resistance in Africa was initially undertaken via the U.S. National Library of Medicine (http://www.ncbi.nlm.nih.gov), supplemented with information available from the reference collection within the insecticide resistance group at the Liverpool School of Tropical Medicine (Liverpool, United Kingdom).

In Africa, there are >140 recorded species of *Anopheles*, of which at least eight are vectors of disease (Gillies and DeMeillon 1968, Gillies and Coetzee 1987). Research has concentrated on the major vectors, predominantly *Anopheles gambiae* (Patton) and *Anopheles arabiensis* (Patton), which are often abundant in the field and relatively easy to rear and colonize. More recently, there has been an increase in the number of studies on *Anopheles funestus* (Giles) in southern Africa (Casimiro et al. 2006b), although this species remains very difficult to colonize.

To collate the data, a relational database was constructed using Access 2000. The locality from which the insects were collected was recorded in decimal degrees to a minimum of two decimal points. Where coordinates were not published, or maps were not provided to allow digitization, the study location data were obtained from the author or failing this via world atlas (http://www.worldatlas.com). Reports from localities where it was not possible to obtain coordinates were discarded. *An. gambiae* and *An. funestus* are species complexes, and in the early literature mosquitoes are often listed only as *An. gambiae* complex or *An. funestus* group. Hence, some of the earlier insecticide resistance data could not be allocated directly to the species level. Because of this difficulty, the data for all *Anopheles* were pooled to view temporal resistance patterns. Similarly, because of the historical nature of the published references different methodologies were used to collect resistance data. To standardize data, information on resistance was translated into the presence or absence of resistance at any given location.

Table 1. Number of sites reporting insecticide resistance in Africa for each 5-yr period from 1956 to 2003.

Yr	No. sites
1956–1960	7
1961–1965	4
1966–1970	10
1971–1975	1
1976–1980	
1981–1985	5
1986–1990	5
1991–1995	24
1995–2000	80
2000–2005	22

Results

Insecticide resistance is not a new phenomenon, with published African malaria vector insecticide resistance data covering a 50-yr span. DDT resistance was initially documented in 1956 (WHO 1957), just 11 yr after its introduction (Mabaso et al. 2004). However, routine monitoring of resistance levels in Africa was never initiated, and the sporadic monitoring that occurred in the 1960s and early 1970s was later discontinued. This lack on monitoring is reflected in the numbers of published articles on insecticide resistance. Now, with increased ITN and IRS operations in Africa, resistance monitoring has restarted in many countries, although it has been hampered by a lack of trained personnel able to undertake even the most basic resistance testing. This was partially rectified in 1996 through the Multilateral Initiative on Malaria (MIM), which funded three insecticide resistance-monitoring programs in eastern, western, and southern Africa. These programs facilitate north–south and south–south linkages and incorporated training with extensive resistance monitoring. Subsequently, there was an increase in publications from several groups who had benefited from this training effort.

Table 1 gives the number of studies for which resistance data were collected over different times and the total number of field sites represented. A summary of the data that could be georeferenced is given in Table 2. There is a bias within the database because of the systematic underreporting of susceptibility to insecticides. Susceptibility data are generally only reported in studies where insecticide resistance is subsequently found (Vulule et al. 1996, Hargreaves et al. 2003).

Table 2. Summary of the numbers of published articles with insecticide resistance reports in anopheline mosquitoes that could be georeferenced

Yr	*An. gambiae* s.l.	*An. gambiae* s.s	*An. arabiensis*	*An. funestus*	*An. melas*	*An. pharoensis*
1956–1960	2					
1961–1965	3	2				
1966–1970	1	1	2			
1971–1975		1				
1976–1980						
1981–1985	2		1	1		
1986–1990	3	1	3			
1991–1995	6	3	2		1	
1995–2000	6	10	2	1	1	
2000–2005	4	6	2	1		1
Total no. of articles	27	24	12	3	2	1

A prototype African malaria decision support system has already been developed to support malaria control operations in Mozambique by the Medical Research Council in South Africa. This is a malaria information system in an interactive, flexible GIS-based format. It is linked to the mapping malaria risk in Africa (MARA) database (http://www.mara.org.za). The published insecticide resistance data collated during this study was linked to this system presented in Fig. 1.

Because of the difficulty of ascertaining the exact insecticide-resistant species within a complex within the early literature, the data for all *Anopheles* are pooled in the maps. Where available, full details of the complex or species level data are available from the reference lists in the supporting on line material (http://www.mara.org.za). The online material also includes maps of resistance, tables of references, and coordinates used to generate these maps.

Historically, resistance reports were based on bioassays using standard WHO discriminating dosages with insecticide-impregnated filter papers to assess mortalities of adult Anopheles (WHO 1998). The WHO discriminating dosages are set at double the dose that gives 100% mortality of a range of susceptible anopheline species. As such, these assays will only detect significant levels of resistance (more than twofold), but they cannot (with the potential exception of the dieldrin bioassays with 4% and 0.4% papers) be used to accurately monitor resistance gene frequencies. For the purposes of this analysis, 3–100% survival after exposure to the discriminating dosage of insecticide for the recommended time period was taken as evidence of resistance in the population tested. Later reports of resistance often take a mechanistic approach by using biochemical and/or molecular (polymerase chain reaction)-based assays for resistance monitoring. The database has been configured to accept data generated from all three monitoring methods.

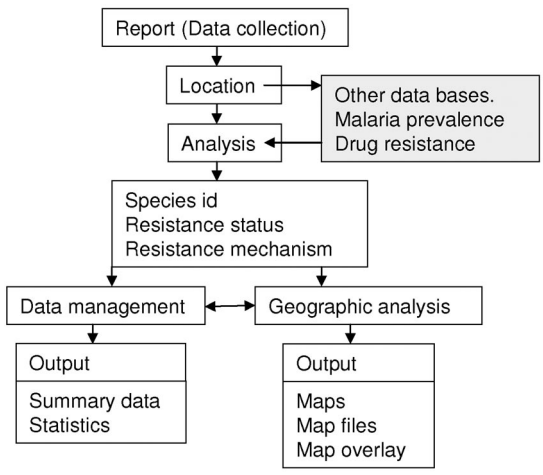

Fig. 1. Simplified structure of the insecticide resistance monitoring database.

The first reports of insecticide resistance to mainstream insecticides in African Anopheles were to DDT and dieldrin in 1956 in *An. gambiae* s.l. specimens collected from Nigeria (Figs. 2 and 3). Although the numbers of reports of resistance have risen steadily with more rapid increases in West Africa, the number of sites sampled has remained relatively restricted (Fig. 3). The clustering of sites in a small number of localities is driven more by the choice of field sites from which a small number of entomological research teams operate rather than reflecting the real extent of the insecticide resistance problem within African *Anopheles.* The greatest increase in the number of localities at which resistance was analyzed occurred between the 1960s and 1970s. At this time, a major cluster of West African sites, including localities in Burkina Faso, Cote D'Ivoire, The Gambia, and Nigeria, were established. Along with a much smaller number of sites along the east African border, including, Kenya, Tanzania, and South Africa. No studies on insecticide resistance in vectors for Central Africa and on the West Africa border below Cameroon have been published. The establishment of the African Network on Vector Resistance (ANVR), which aims to sample at least two localities in every African country, should start to rectify this sampling bias and produce a much better geographical overview of the current resistance situation. Data from this exercise, once it becomes publicly available, will be incorporated into the current database.

The bulk of the insecticide resistance reports concerned DDT, dieldrin, or pyrethroids. DDT and diel-

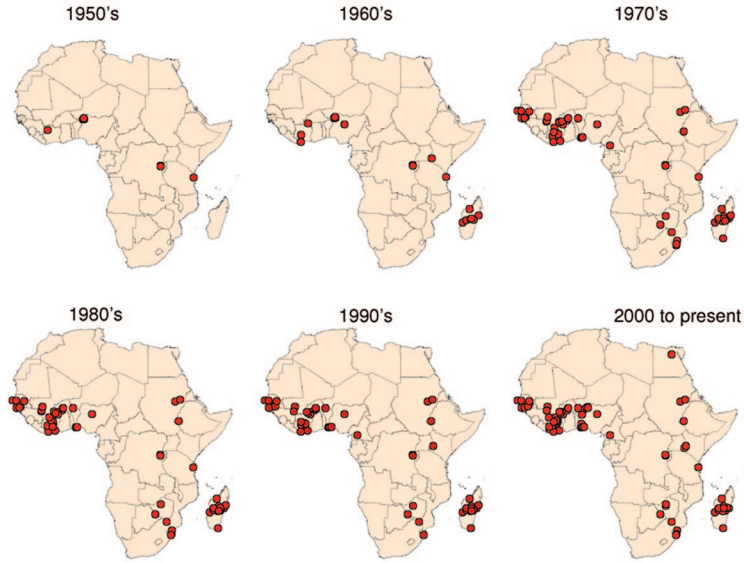

Fig. 2. Time series showing the sites that have reported insecticide resistance. (Locality of study site. Sites are plotted based on year of publication.)

drin were introduced for malaria control in several African localities in the late 1940s and were the predominant insecticides in use from 1955 to 1969 (Trigg and Kondrachine 1998). As resistance to DDT and dieldrin increased, along with concerns over potential environmental impacts of these insecticides, there was a shift to alternative insecticides. Organophosphates were used briefly for indoor residual house spraying in a small number of localities, for example, the Gezira cotton-growing regions of Sudan, but in Africa the volume of these insecticides for public health never reached the levels of DDT use. With the increasing trend of insecticide-impregnated bed-net use, interest in monitoring pyrethroid resistance increased. Although these insecticides have had only limited IRS treatment use in Africa.

Earlier use of DDT also left the potential legacy of cross-resistance between DDT and pyrethroids, through alterations in their common target site, the sodium channel. Most reports of *kdr* resistance in *Anopheles* come from West Africa, where the use of DDT in agriculture probably contributed to the orig-

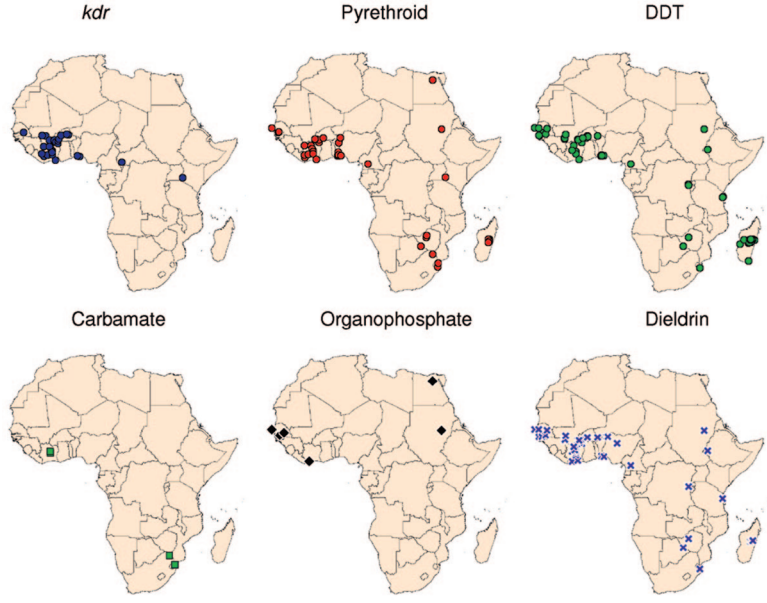

Fig. 3. Location and insecticide resistance reports for *Anopheles* species in Africa.

inal selection of this resistance mechanism (Mouchet 1988). The only confirmed report of *kdr* outside of West Africa comes from Kenya, where a different mutation has been found in the sodium channel (Ranson et al. 2000). Monitoring of the *kdr* resistance mechanism was greatly facilitated by the establishment of the mutations within the sodium channel gene that confer the resistance phenotype. Conversely, the difficulty in monitoring metabolic pyrethroid resistance has potentially resulted in an under reporting of metabolic resistance in *An. gambiae.* However, understanding the intricacies of resistance mechanisms and cross-resistance will greatly facilitate rational insecticide choice in vector control programs. To achieve routine operational monitoring and remove the bias from the data generated by the ease of monitoring different mechanisms, simple informative platforms are required for monitoring all resistance.

Some organophosphates and carbamates are recommended for IRS (White 1999, Guillet et al. 2001); therefore, an understanding of the spatial distribution of resistance to these insecticides is needed. Few sites exist within Africa (eight for carbamates and 13 for organophosphates) where resistance is reported to either of these insecticide groups (Fig. 3); however, this may be related to their limited use in large-scale vector control to date in Africa and possibly due, in part, to a lack of resistance monitoring.

Discussion

As malaria vector control activities in Africa increase, rationale choices of insecticide from an evidence base will become more critical if scarce resources are to be optimally deployed. The traditional method of using an insecticide until resistance becomes the limiting factor and directly results in an increase in disease transmission is no longer sustainable. However, to react to resistance before this point, a realistic operational monitoring and evaluation protocol for insecticide resistance in malaria vectors needs to be established. A collated database of published information is now freely available on the MARA/Atlas du Risque de la Malaria en Afrique (ARMA) Web page in the format of maps and spread sheets. Linking this database to existing malaria databases in a GIS platform has created a simple decision support system for vector control programs that will generate information essential to effective insecticide policy at country level. A proposal for the development of such a resource was initiated at the MIM Insecticide Resistance workshop in 2001 (Sina and Aultman 2001), and this is now being developed on an operational scale as part of the Innovative Vector Control Consortium (IVCC) recently funded by the Bill and Melinda Gates Foundation (Hemingway et al. 2006).

The incorporation of insecticide data into a robust decision support system for malaria requires the reporting of both susceptibility and resistance data to allow evidence-based decisions for control. To remove the data bias generated by investigators working in limited sites, a community-based sentinel site system is being established in a number of countries to generate these data. This simple system requires limited resources and has been successfully piloted operationally in Mozambique. Similar systems have already been adopted for malaria prevalence (Clarke et al. 1996) bringing research and malaria control programs together (Martin et al. 2002).

WHO bioassays are good indicators of the presence of high level (2–100-fold) resistance in mosquito populations, but they cannot be used either to measure gene frequency accurately or suggest the epidemiological impact of resistance. Resistance gene frequency in general will be higher than indicated by bioassay data alone (Casimiro et al. 2006a,b), particularly where resistance monitoring is undertaken on field-caught *Anopheles* of indeterminate age. Hence, bioassays are not sufficiently sensitive to monitor low level resistance. As new molecular technologies are developed, resistance monitoring will become more sensitive (David et al. 2005), making resistance management a more realistic goal. These new methods, in contrast to bioassays, will identify the underlying resistance mechanisms. This is beneficial as many resistance mechanisms give cross-resistance to multiple insecticides (Hemingway and Ranson 2000), hence defining the resistance mechanism, should improve the predictive value of the malaria vector control data.

Given the renewed impetus in regard to large-scale malaria control, driven largely by the resources being made available by the GFATM, there is a renewed urgency to develop this resource, which is central to evidence-based insecticide use policy. The benefits of evidence-based insecticide policies in vector control have been established in Sri-Lanka (Kelly-Hope et al. 2005), Mexico (Hemingway et al. 1997), and Mozambique (Casimiro et al. 2006a,b). The IVCC program will extend the pilot entomological decision support system described here and incorporate data on insecticide resistance, vector density, and infectivity. These data will enable evaluation of intervention efficacy and support vector control policy.

Acknowledgments

We thank H. Ranson and N. Hawkes for comments on the manuscript. This work was funded by the Gates Malaria Partnership funded by the Bill & Melinda Gates Foundation.

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Received 29 November 2005; accepted 7 April 2006.