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RECENT ADVANTAGES IN INSECTICIDES FOR MALARIA PROGRAMS

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Insecticides, particularly DDT, continue to be the mainstay in malaria programs. However, the specter of failure because of insecticide resistance has led to considerable research on substitute materials. ~~These~~ substitutes may be used as resi~~dual~~ applications, space sprays, and/or larvicides. The steps in selecting these compo~~unds~~ go from initial screening to determine biological activity to large-scale field trials which may include epidemiological assessment.

Residual type compounds currently being evaluated include organophosphorus compounds such as fenitrothion, iodofenphos, phenthoate, phoxim and chlorphoxim, and carbamates such as propoxur, carbaryl, Mobam and Landrin.

Chemicals for use as space sprays include malathion, naled, fenthion, and others. Larvicidal compounds include Abate, chlorpyrifos, and methyl Dursban in addition to some of the aforementioned compounds.

Malathion, propoxur, and fenitrothion are the compounds that should receive initial consideration for use against vector populations resistant to DDT residual applications. The pesticide of choice as a space spray is malathion; as a larvicide, Abate. As a solution to the control of vectors that transmit malaria through outdoor biting, it appears logical that the chemical control measures employed in the future may include all three types of application.

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Insecticides have been, and continue to be, the mainstay of the global program to eradicate malaria. Their primary use has been as an adulticide treatment applied to the interior of occupied dwellings. Other techniques for applying insecticides have received little attention until recent years when it became apparent that the residual spray methodology was not successful in coping with the malaria problem in certain parts of the world. Some of this failure may be attributed to the physiologic resistance that developed in the populations of certain anopheline vectors to the chlorinated hydrocarbon insecticides commonly used in eradication programs. However, malariologists agree that physiologic resistance *per se* has not been a critical factor in disrupting the overall eradication effort except in specific problem areas such as the Middle East where the vectors are resistant to both dieldrin and DDT.

Insecticides represent an effective tool only when contact occurs between the insect and the chemical. Therefore, when the behavior of the mosquito limits or prevents such contact, the treatment is of little or no value. Since residual sprays are applied principally to the interior of homes it is readily understandable that malaria prevails when the vector bites the people out-of-doors or when it fails, after biting within the dwelling, to rest on the treated walls long enough to absorb a toxic dose of the chemical. Under such circumstances the failure of the insecticide applications lies not in the chemical but in the circumstances, a fact which is sometimes overlooked by those whose programs do not achieve success.

The major origin of new pesticides is commercial sources, and the compounds are sought in relation to their agricultural, not public health value, primarily because of the economics involved. Regardless of their ultimate use, the new materials undergo a series of evaluations from laboratory to field before they are considered ready for operational application. Each succeeding stage of tests imposes more exacting criteria on the compound as to its safety and to its efficacy against the vector species.

The steps involved in the programs of insecticide evaluation by the World Health Organization (WHO) and the Agency for International Development (AID) are: 1) initial screening to determine the toxicity of the compound to insects; 2) laboratory evaluation of selected candidate insecticides using reared insects; 3) simulated field studies using laboratory reared insects but with the tests conducted out-of-doors; 4) small-scale field studies in which naturally occurring insects are used in the evaluation; 5) field tests over an expanded area, such as a residual treatment of a village or larvicidal treatment of an extensive breeding site; 6) a large-scale field trial which would involve the residual spraying of several thousand houses followed by entomologic and toxicologic assessment; and 7) a final field trial in which 200,000 or more homes would be sprayed, the efficacy of which would be determined by epidemiological assessment.

RESIDUAL APPLICATIONS

Although DDT, dieldrin, and lindane represent the compounds longest in use as residual sprays, only DDT is of primary importance today. Research-wise most of the effort has been to explore for effective substitutes among chemical groups other than organochlorine materials. Malathion and fenthion were among the earliest organophosphorus materials which proved to be effective against malaria vectors. The initial field studies on these materials began in 1959 in El Salvador where each chemical was shown to provide 2.5 to 3 months of effective kills of *Anopheles albimanus* at a dosage of 2 g/m^2.[1] Later, when fenthion was tested in Iran, it was found to pose a toxicologic hazard and was, therefore, not suitable for house application.[2] However, malathion was accepted as a suitable substitute for DDT when studies in

Uganda showed that 2 g/m² were capable of interrupting malaria transmission.[3] Since that time, developments have centered about other organophosphorus compounds such as fenitrothion (OMS-43), iodofenphos (OMS-1211), phenthoate (OMS-1075), phoxim, (OMS-1170), chlorphoxim (OMS-1197), and various carbamate materials, propoxur (OMS-33), carbaryl (OMS-29), Mobam* (OMS-708), and Landrin (OMS-597).

Current information on new insecticides to be discussed relates to village scale trials of OMS-597 and 1211 and to a Stage VI study of OMS-43 performed by WHO in Africa.

OMS-597 (Landrin)

This carbamate was tested in 1967,[4] and again in 1969.[5] In the 1967 trial, an application rate of 2 g/m² resulted in excellent control of *Anopheles gambiae* and *Anopheles funestus* for 90 days; however, the data from bioassays indicated a relatively short residual life, and problems of mixing, nozzle erosion, and sedimentation were encountered with the formulation.

In 1969, a village of 102 houses was treated with an improved formulation of OMS-597 at a dosage rate of approximately 2.4 g/m². After treatment, the house resting indices for *A. gambiae* per hut, as measured by pyrethrum spray and exit trap collections, ranged from 0 to 3.2 for 148 days. The man–*A. gambiae* contact index indoors up to the 59-day evaluation period was not more than 2.3 bait night in the treated area versus 20 to 40 bait night in the untreated village. The same index for *A. funestus* was not more than 0.8 bait night in the treated village and 14 to 68 bait night in the unsprayed village. These marked reductions in man–mosquito contacts thus indicated a considerable decrease in the comparative risk of malaria infection. Bioassays showed kills of more than 70% for 116 and 79 days on mud and thatch surfaces, respectively.

The 1969 trial showed OMS-597 to be highly effective biologically for 4 months. No operational difficulties were encountered, nor was any adverse clinical effect detected among the spraymen or villagers.

In El Salvador, the Central America Malaria Research Station (CAMRS) is conducting a small-scale village trial with OMS-597 against *A. albimanus* and the results to date are promising.

OMS-1211 (iodofenphos)

This organophosphorus compound was evaluated in 1970 in Nigeria in an experiment which included two treatments in each of two villages.[6] Both treatments were at a rate of approximately 1.9 g/m², 11 weeks apart. The results showed a definite reduction in the house resting densities of *A. gambiae* and a long term effectiveness of the treatments on mud and thatch surfaces. In addition, there was a marked difference in the man-mosquito contact between sprayed and unsprayed houses. In sprayed houses, the contact index ranged from 3.0 to 18.5 bait night during 56 days after the second treatment. Moreover, surviving females appeared in exit traps as early as 24 days after treatment in the 1st round and 15 days after treatment in the 2nd round.

Because of the findings on surviving females and the man–mosquito contact indices, the epidemiological efficacy of OMS-1211 appears limited. Nonetheless, since the compound is safe for indoor house spraying and has shown long term effectiveness on mud and thatch, it may prove to be suitable for use in other areas against different anopheline species.

OMS-43 (fenitrothion)

This organophosphorus compound was under intensive investigation for several years in Kisumu, Kenya;[7] ecological and baseline studies were carried out for 1 year before the spraying began. The project area contained more than 2,800 scattered compounds and approximately 21,000 individuals. OMS-43 was applied at a dosage rate of 2 g/m², and four cycles of spraying were made over the project area. Because *A. funestus* is more drastically affected by residual applications than *A. gambiae*, only the latter species will be discussed.

A. gambiae was prevalent in both the operational area (120 specimens/hut) and the comparison area (92 specimens/hut) during the prespray period. After spraying, 1 specimen/hut indices from the pyrethrum spray collections occurred relatively soon—11 to 39 days after the 2nd spray round. However, all of the increases in the house resting indices in the sprayed area were related to, but lagged behind, population rises in the comparison area. Apparently when natural den-

* Use of trade names is for identification purposes only and does not constitute endorsement by the Public Health Service or the U.S. Department of Health, Education, and Welfare.

sities were high in the surrounding unsprayed areas, infiltration was sufficient to bring house-resting indices above 1/hut in the sprayed zone. Average house-resting densities for the sprayed area for the four cycles were 2.8, 5.3, 3.6 and 0.6; for the sprayed area the indices were 123, 247, 79 and 72.

Observations further indicated that large proportions of the mosquitoes taken in pyrethrum spray collections entered the houses after feeding and that such movement probably occurred at dawn. Since spray collections were carried out between 7:30 and 9:00 AM the data were biased, because the number of adult mosquitoes that entered the houses in the early morning did not receive sufficient exposure to the insecticide to be knocked down even though they may have acquired a lethal dosage within that exposure time.

The maximum man-*A. gambiae* indices ranged between 0.2 and 0.8/bait night in the treated index area, whereas in the comparison area the index ranged from 0.6 to 18.4/bait night.

From these studies, it was concluded that the four applications of OMS-43 at 3-month intervals in the Kisumu area adequately controlled *A. gambiae* and *A. funestus*. In view of these entomological findings, OMS-43 is now considered a suitable candidate for an extensive epidemiological trial.

OMS-33 (propoxur)

This carbamate insecticide has been evaluated in Southern Iran and Northern Nigeria where it provided 3 to 4 months control of the vector involved.[8]

In a test in El Salvador (1966–67) seven rounds of spraying were conducted in an area containing 3,000 houses and 13,500 inhabitants. The period of effectiveness of OMS-33 against DDT- and dieldrin-resistant *A. albimanus* populations varied from 6 to 14 weeks: in most villages near intensive breeding sites, effectiveness ranged from 8 to 10 weeks.[8]

SPACE APPLICATIONS

Treatments of this type have long been used in mosquito control in the United States, but the feasibility of their use in malaria eradication programs remains undetermined. However, the occurrence of extradomiciliary transmission raises the question as to whether such treatments are desirable in situations where the use of residual house sprays is only partially effective in curbing transmission.

Ground treatments are dispersed as thermal or nonthermal fogs where n the insecticide is formulated in fuel oil or water emulsions or as ultra low volume (ULV) treatments in which the concentrated insecticide is dispersed. The chemicals used as fogs are organophosphorus compounds such as malathion, naled, and fenthion. Malathion is probably the most widely used and is highly effective against adult mosquitoes.

Of the newer compounds tested, thermal and nonthermal aerosol materials such as chlorpyrifos, propoxur, phoxim, and chlorphoxim offer promise.[9,10] These materials at concentrations of 2 to fluid oz per gallon of fuel oil or water gave 91% or greater kills of caged *A. albimanus* at 150 feet. Other compounds, such as Abate, an extremely potent larvicide, are ineffective as space sprays.

Malathion is presently the only compound approved in the United States for ground-applied ULV treatment. However, in comparative tests with caged adult mosquitoes fenitrothion, methyl Dursban, and chlorpyrifos have been shown to be superior to malathion.[11]

With aerially applied ULV applications, compounds such as malathion, fenthion, and naled have been used. However, only malathion and naled are now labeled in the United States for such treatments since the label for use of fenthion in this manner has been withdrawn. The compounds mentioned previously for ground ULV treatments also may have potential for aerial usage.

The preceding information on residues and space sprays concerns investigations of those experimental compounds that have progressed to the levels where they are now ready for epidemiological evaluation or for advanced entomologic and toxicologic assessment. However, the present-day concern about DDT and insecticide use in general necessitates a look at what is happening at the earlier stages of experimentation with pesticides.

New materials are still being synthesized by commercial sources but it has been apparent that the number of new compounds emerging from such sources has declined over the past few years. However, there has been an upswing in efforts to develop biodegradable pesticides, particularly analogues of DDT. Whether or not such anasities were high in the surrounding unsprayed areas, infiltration was sufficient to bring house-resting indices above 1/hut in the sprayed zone. Average house-resting densities for the sprayed area for the four cycles were 2.8, 5.3, 3.6 and 0.6; for the sprayed area the indices were 123, 247, 79 and 72.

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LARVICIDES

Larvicide treatments have played an extremely minor role in malaria eradication programs, principally because of logistical and cost problems. Where residual spraying has failed to do the job or in situations where larviciding appears to be a more efficient method of curbing anopheline densities, consideration has been given to its potential.

A number of compounds are effective against mosquito larvae, the majority being organophosphorus materials such as Abate, chlorpyrifos, methyl Dursban, and fenitrothion. In addition, petroleum oils have regained a role in mosquito larviciding because of the resistance problem. Although the use of these chemicals has been mainly against culicine species, the same pesticides are also toxic to anopheline larvae. The principal difficulty in their use against *Anopheles* lies in how to apply the larvicide effectively and economically. Nonetheless, Abate has been used effectively in the United States for control of anopheline larvae in the lakes of the Tennessee Valley Authority at a dosage of 0.004 lb/acre. In Jordan, Abate has been applied successfully against *A. sergenti* and *A. superpictus*, while in Africa limited trials indicate that 2.0 ppm of Abate kept ponds free of anopheline larvae for more than 35 days.

It is also obvious that the use of larvicides for anopheline control would greatly increase the possibility of harming nontarget organisms, which is not a critical factor with the current practices of using adulticides in malaria eradication.

Among the new developments in mosquito larvicides is the possible use of juvenile-type hormones for this purpose. At Savannah, tests with 25 juvenile-type hormones against mosquito larvae have shown that these materials affect the development of the insect by preventing adult emergence or by producing deformed adults incapable of normal functioning.[14,15] Some compounds exert their effect in the 4th larval instar and in the pupae; others allow the adults to emerge but they cannot fly or walk. One material produces its effect during the change from larva to pupa. The pupae are not melanized and stretch out rather than assume their normal question mark shape. The mature larvae are most affected by the treatment: exposure of first or second instar larvae may not result in any marked deleterious effect. Dosages in ppm for the LC-95 levels range from 0.1 to as low as 0.0025.

DISCUSSION

At the present time and for the foreseeable future, insecticides remain the major weapon in the worldwide attack against malaria. The principal use of these chemicals is as a residual application inside homes. Malathion, propoxur, and fenitrothion appear to be the compounds that should receive first consideration in areas where DDT has not been successful because of vector resistance. Before deciding on such substitute compounds, the possibility that the vector may also be resistant to one or more of the candidate compounds must be recognized. Such insecticides may already have been used extensively for agricultural purposes and this use may have led to the development of such resistance. There is a strong possibility that the resistance of *A. albimanus* to malathion in El Salvador may have developed through this route.[16] Further, the exposure of a mosquito population to one com-