Dichlorodiphenyltrichloroethane (DDT) for Indoor Residual Spraying in Africa: How Can It Be Used for Malaria Control?

Shobha Sadasivaiah,† Yeşim Tozan,‡ and Joel G. Breman*  
Weill Cornell Medical College of Cornell University, Cornell University, New York, New York; Earth Institute, Columbia University, New York, New York; and Fogarty International Center, National Institutes of Health, Bethesda, Maryland

Abstract. In 2006, the World Health Organization issued a position statement promoting the use of indoor residual spraying (IRS) with dichlorodiphenyltrichloroethane (DDT) for malaria vector control in epidemic and endemic areas. Other international organizations concurred because of the great burden of malaria and the relative ineffectiveness of current treatment and control strategies. Although the Stockholm Convention of 2001 targeted DDT as 1 of 12 persistent organic pollutants for phase-out and eventual elimination, it allowed a provision for its continued indoor use for disease vector control. Although DDT is a low-cost antimalarial tool, the possible adverse human health and environmental effects of exposure through IRS must be carefully weighed against the benefits to malaria control. This article discusses the controversy surrounding the use of DDT for IRS; its effective implementation in Africa; recommendations for deployment today, and training, monitoring, and research needs for effective and sustainable implementation. We consider the costs and cost effectiveness of IRS with DDT, alternative insecticides to DDT, and the importance of integrated vector control if toxicity, resistance, and other issues restrict its use.

INTRODUCTION

Although malaria has been successfully eradicated in high-income and many middle-income countries, the disease remains a major health problem in poor nations. This disease wreaks havoc in Africa, where the majority of the global malaria incidence (70% of clinical Plasmodium falciparum cases) is concentrated.1 It was estimated that 18% of child deaths were directly attributable to the disease in this region in 2000.2 Malaria is ranked second after human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and accounts for an estimated 10% of the total disease burden on this continent;3 a recent study showed that coinfection fuels the spread of both diseases and results in excess HIV infections and clinical malaria episodes.4 In addition to its direct health impact, the disease imposes a huge economic burden on afflicted nations through high healthcare costs, missed days of work and school, reduced economic productivity and output, and low levels of foreign investment.5

The enormous toll that malaria takes on the world’s poorest and most vulnerable populations require all proven and cost-effective interventions be deployed to battle this scourge. Malaria control efforts are driven by the persisting health and economic burden of the disease. However, restricted impact on disease transmission of the current patient management and preventive strategies (e.g., insecticide treated nets [ITNs]) limits progress toward internationally set malaria goals and targets and poverty reduction.6 Indoor residual spraying (IRS) with dichlorodiphenyltrichloroethane (DDT) is now reentering the armory of malaria endemic countries and international organizations committed to controlling the disease. This article reviews the role of IRS with DDT in malaria vector control, clarifies a place for DDT as a residual insecticide among alternatives, and raises operational and technical issues for consideration when using DDT for IRS.

HISTORY

After the discovery of the insecticidal properties of DDT in 1939, further testing of the insecticide was conducted at the U.S. Department of Agriculture’s laboratory in Orlando, Florida, in 1942 and 1943.7 The tests confirmed the practical value of DDT in disease vector control, and the insecticide was first used by the military personnel in southern Italy in 1944 and in other parts of the world in the final years of World War II.8 In 1945, DDT was introduced as a vector control measure in civilian populations in Guyana and Venezuela9,10 and then in 1946 in Cyprus and Sardinia.9 Although large-scale use of DDT for disease vector control started in 1946,11 the insecticide had been intensively applied for agricultural pest control since 1940.12

The astonishing impact of DDT on mosquito longevity resulted in successful early campaigns against the malaria vector. Calls for the global eradication of malaria followed.13 In addition, many field studies consistently provided evidence that the primary effect of DDT is its excitoto-repellency, deterring entry into or driving mosquitoes out of sprayed houses and reducing transmission with lower feeding rates and shorter resting periods.14 There was a marked reduction in the mean age of mosquito population as measured by the number of ovarian dilatations and a 86% reduction in the sporozoite inoculation rate after the introduction of IRS with DDT in a holoendemic area of Tanzania.15

In 1955, the World Health Organization (WHO) launched the Global Malaria Eradication Campaign based on the periodic use of IRS with DDT for 3–5 years to interrupt malaria transmission.16 This time-limited attack phase would have been followed by active case detection and surveillance to prevent disease propagation.16 Weak healthcare systems, insufficient administrative, operational, and technical capacity, and public reaction to spraying were the major factors contributing to the demise of national eradication programs.13 However, it was the development of Anopheline resistance to DDT that was primarily responsible for the dwindling political and financial support for the global campaign.13 The eradication period ended in 1969, and the eradication strategy was replaced by a longer-term disease control strategy as part of the growing primary healthcare movement of the 1970s.13

† The first two authors contributed equally to this manuscript.
* Address correspondence to Joel G. Breman, Fogarty International Center, National Institutes of Health, Bethesda, MD. E-mail: jbreman@nih.gov
Although the Global Malaria Eradication Campaign did not achieve its ultimate objective, it was credited with eliminating the risk of disease for about 700 million persons, mainly in North America, Europe, the former Soviet Union, all Caribbean islands except Hispaniola, and Taiwan.\textsuperscript{17} High socio-economic status, well-organized healthcare systems, and relatively less intensive or seasonal malaria transmission were the main factors in attaining the disease elimination goal in these regions.\textsuperscript{16} Malaria was effectively suppressed in sub-tropical and tropical areas of Asia, Latin America, and the Middle East.\textsuperscript{17} Notable among those efforts was the near eradication of malaria in India, where the annual number of malaria cases was reduced from an estimated 75 million to about 100,000 in the early 1960s.\textsuperscript{18} These reductions were not sustained after the eradication period because limited resources were devoted to malaria control. Because of the perceived intractability of the disease and concerns about infrastructure and sustainability, large swaths of Africa were left out of the global eradication efforts.\textsuperscript{13} Yet several African countries embarked on pilot projects of IRS with DDT and dieldrin with the assistance of WHO and the United Nations Children’s Fund from between the 1940s and 1960s.\textsuperscript{19–21} Although malaria transmission was not interrupted in areas with intense and stable transmission (holoendemic to mesoendemic zones) with tropical climates, malaria vectors and prevalence rates were considerably reduced during these projects (e.g., in Cameroon, Kenya, Liberia, Nigeria, Senegal, and Tanzania).\textsuperscript{19–21} In areas with seasonal and unstable transmission (hypoendemic) with subtropical and temperate climates, IRS projects interrupted transmission in vast territories and eliminated the disease at the limits of tropical Africa.\textsuperscript{20} Malaria eradication programs were implemented on the islands of Zanzibar and Pemba, and the pilot projects were scaled up to national level in South Africa, Swaziland, Zimbabwe, and the islands of Madagascar, Mauritius, and Réunion.\textsuperscript{20} With the publication of \textit{Silent Spring} by Rachel Carson in 1962, the safety of DDT for human health and the environment was challenged. Before DDT was officially banned in the United States in 1972, it was registered for use in 334 agricultural products.\textsuperscript{12} Driven by the expansion of commercial agriculture, large areas in India and the Central American countries were intensively treated with DDT in the 1960s and 1970s where national eradication campaigns were also operational.\textsuperscript{22} Between 1940 and 1973, estimates indicated that more than 2 million tons (4 billion pounds) of DDT were used in the United States, about 80% of them in agriculture, and some level of resistance was reported in populations of 98 species of economically important insects.\textsuperscript{12} Because of the growing environmental concerns, the agricultural use of DDT diminished rapidly from the 1970s onward, affecting use of the insecticide for public health. DDT for disease vector control was never banned but international pressure restricted its implementation in malarious countries. In the late 1990s, an intense debate erupted when negotiations for global elimination of DDT were initiated by the United Nations Environment Program (UNEP) against a background of an increasing malaria burden.\textsuperscript{23} In 2001, the Stockholm Convention on Persistent Organic Pollutants classified DDT as restricted (Table 1) and allowed a provision for its continued use for disease vector control following the WHO guidelines when “locally safe, effective, and affordable alter-natives are not available.”\textsuperscript{24} This provision was approved without any objection by approximately 150 national delegations,\textsuperscript{25} including those from Southeast Asia where the use of DDT was discontinued in malaria control efforts. Although used in the Americas and Asia, vector control has been neglected as an intervention strategy against malaria in most of Africa.

Today, the WHO actively promotes the use of IRS with DDT (Table 2) and recommends implementation in essentially all epidemiologic settings, including unstable, epidemic-prone areas; stable-endemic areas with seasonal transmission; and stable-hyperendemic areas with seasonal or perennial transmission.\textsuperscript{26} In this strategy, DDT is sprayed on the walls and other surfaces inside dwellings where female \textit{Anopheles} mosquitoes land and rest before or after a blood meal. The WHO currently recommends a standard dosage of 1–2 g active ingredient per m\textsuperscript{2} every 6 months.\textsuperscript{27} Sufficient contact with DDT-sprayed surfaces kills malaria vectors. More importantly, DDT has an excitorepellent effect, deterring entry into and promoting exit from sprayed dwellings.\textsuperscript{14} It is argued that the combined mosquito toxicity and excitorepellent effects of DDT may maintain its continued efficacy in areas where there is resistance against it.\textsuperscript{14,25} A recent study from India assessing the impact of IRS with DDT on malaria transmission corroborated the results of earlier Indian studies reporting marked reductions in vector densities and malaria incidences although the targeted malaria vector had a reduced susceptibility to DDT.\textsuperscript{28}

The gains resulting from IRS activities in Africa between the late 1940s and the 1960s had not been widely documented because most of these projects were viewed as a failure when assessed against a goal of interruption of malaria transmission.\textsuperscript{29,30} During the past decade, IRS has been implemented successfully in southern African countries, and DDT has been used successfully for IRS in Mozambique, South Africa, and in parts of Swaziland, Eritrea, Ethiopia, and Madagascar.\textsuperscript{21,30} Key public health organizations and international development agencies, including the WHO, the United States Agency for International Development, and the World Bank, have recently announced plans to support IRS activities in malaria endemic countries.\textsuperscript{11}  

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The 12 persistent organic pollutants targeted by the Stockholm Convention on Persistent Organic Pollutants\textsuperscript{24–29}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>Class</td>
</tr>
<tr>
<td>Aldrin</td>
<td>Organochlorine insecticide</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>Organochlorine insecticide</td>
</tr>
<tr>
<td>Endrin</td>
<td>Organochlorine insecticide</td>
</tr>
<tr>
<td>Chlordane</td>
<td>Organochlorine insecticide</td>
</tr>
<tr>
<td>Heptachlor</td>
<td>Organochlorine insecticide</td>
</tr>
<tr>
<td>Hexachlorobenzene</td>
<td>Organochlorine insecticide</td>
</tr>
<tr>
<td>Mirex</td>
<td>Organochlorine insecticide</td>
</tr>
<tr>
<td>Toxaphene</td>
<td>Organochlorine insecticide</td>
</tr>
<tr>
<td>DDT</td>
<td>Organochlorine insecticide</td>
</tr>
<tr>
<td>Polychlorinated biphenyls</td>
<td>Industrial chemical</td>
</tr>
<tr>
<td>Dioxins</td>
<td>Combustion byproduct</td>
</tr>
<tr>
<td>Furans</td>
<td>Combustion byproduct</td>
</tr>
</tbody>
</table>

\* DDT, dichlorodiphenyltrichloroethane.
On the contrary, an earlier study investigating the effect of DDT on reproductive health showed no significant adverse effects. However, more recent studies have also found that exposure to DDT is associated with higher blood levels of DDT and its metabolites, but no ill effects have been confirmed.

A strong evidence to support this association is that DDT exposure is linked to breast cancer. There is no strong evidence to support this association. Nor is there any indication that DDT has adverse effects on reproductive health. Because of its persistent nature in human adipose tissue and recorded levels in breast milk, neurodevelopmental effects are an important concern. One report indicated that prenatal exposure to DDT was associated with neurodevelopmental delays. Earlier studies investigating the effect of long-term exposure to DDT found no significant excess morbidity among spraymen who worked in eradication programs in India and Brazil for 5 or more years when compared with matched control groups. More recent studies have also shown that persons occupationally exposed to DDT have higher blood levels of DDT and its metabolites, but no ill effects have been confirmed. On the contrary, an earlier study showed that maternal and child health mortality outcomes improved steadily in the coastal areas of Guyana.

**TRENDS IN INSECTICIDE USE FOR VECTOR CONTROL**

Decisions made by the international community regarding the public health use of insecticides are reflected in insecticide use data. Organochlorines, largely DDT, and carbamates are used exclusively for IRS. Synthetic pyrethroids (also used for IRS in the Americas) are the only approved class of insecticides for impregnation of ITNs, and larvicides used in environmental management projects are generally organophosphates. During 1995–2005, the use of DDT and organophosphates for malaria vector control declined steadily (Figure 1), as reported to WHO Pesticides Evaluation Scheme (WHO PES). However, the insecticide use data from South Africa are included only from 2003–2005, and the data from India, where IRS has been the mainstay of vector control for more than 5 decades, were only reported through 2000.

Table 3 gives the recent use of DDT for vector control, as reported to WHO PES during 2000–2005. Use of DDT increased substantially among the African nations during this period. In the Americas, among the 3 nations that reported DDT spraying for disease vector control, DDT use appears to have decreased almost to zero after 2000. This period coincides with Mexico’s decision to discontinue using DDT for malaria vector control, replacing it with synthetic pyrethroids; this followed the signing of the North American Agreement on Environmental Cooperation, a side accord to the North American Free Trade Agreement. In 1997, Mexico committed to phasing out DDT use and production over 10 years but achieved elimination rapidly in 2000. Other Latin American countries were forced to stop using DDT for disease vector control because of this trade agreement and limited availability of the insecticide. Lastly, data regarding the use of DDT in Southeast Asia are limited. Given that India did not report to WHO PES after the year 2000 and that no data were available from China, the total use in this region is likely to be significant.

**SAFETY**

Because it is highly persistent and lipid soluble, DDT bioaccumulates through the food chain. The half-life of dichlorodiphenylchloroethylene (DDE), a primary metabolite of DDT, is about 11 years. For these reasons, intensive agricultural use of DDT from the 1940s to the 1970s led to adverse environmental effects, including acute toxicity to birds. Several reproductive effects have been demonstrated in birds, in particular thinning of egg shells in several species. An association between exposure to DDT and a number of health outcomes in humans has also been proposed. It has been suggested that because of its weak estrogenic activity, DDT exposure is linked to breast cancer; there is no strong evidence to support this association. Nor is there any indication that DDT has adverse effects on reproductive health. Because of its persistent nature in human adipose tissue and recorded levels in breast milk, neurodevelopmental effects are an important concern. One report indicated that prenatal exposure to DDT was associated with neurodevelopmental delays. Earlier studies investigating the effect of long-term exposure to DDT found no significant excess morbidity among spraymen who worked in eradication programs in India and Brazil for 5 or more years when compared with matched control groups. More recent studies have also shown that persons occupationally exposed to DDT have higher blood levels of DDT and its metabolites, but no ill effects have been confirmed. On the contrary, an earlier study showed that maternal and child health mortality outcomes improved steadily in the coastal areas of Guyana.

**TABLE 2**

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>Class</th>
<th>Recommended dosage of active ingredient (g/m²)</th>
<th>Duration of effective action (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDT</td>
<td>Organochlorine</td>
<td>1-2</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Fenitrothion</td>
<td>Organophosphate</td>
<td>2</td>
<td>3-6</td>
</tr>
<tr>
<td>Malathion</td>
<td>Organophosphate</td>
<td>2</td>
<td>2-3</td>
</tr>
<tr>
<td>Pirimiphos-methyl</td>
<td>Organophosphate</td>
<td>1-2</td>
<td>2-3</td>
</tr>
<tr>
<td>Propoxur</td>
<td>Carbamate</td>
<td>1-2</td>
<td>3-6</td>
</tr>
<tr>
<td>Bendiocarb</td>
<td>Carbamate</td>
<td>0.1-0.4</td>
<td>2-6</td>
</tr>
<tr>
<td>Alpha-cypermethrin</td>
<td>Pyrethroid</td>
<td>0.02-0.03</td>
<td>4-6</td>
</tr>
<tr>
<td>Cifluthrin</td>
<td>Pyrethroid</td>
<td>0.02-0.05</td>
<td>3-6</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>Pyrethroid</td>
<td>0.02-0.025</td>
<td>3-6</td>
</tr>
<tr>
<td>Etofenprox</td>
<td>Pyrethroid</td>
<td>0.1-0.3</td>
<td>3-6</td>
</tr>
<tr>
<td>Lambda-cyhalothrin</td>
<td>Pyrethroid</td>
<td>0.02-0.03</td>
<td>3-6</td>
</tr>
<tr>
<td>Bifenthrin</td>
<td>Pyrethroid</td>
<td>0.025-0.05</td>
<td>3-6</td>
</tr>
</tbody>
</table>

*DDT, dichlorodiphenylchloroethylene.

**FIGURE 1.** Quantities of commonly used insecticides for malaria vector control. DDT = dichlorodiphenylchloroethylene; OP = organophosphate (chlorpyrifos, chlorpyrifos-methyl, fenitrothion, fenitrothion, malathion, pirimiphos-methyl, temephos); C = carbamate (bendiocarb, propoxur); PY = pyrethroid (alpha-cypermethrin, bifenthrin, cyfluthrin, cypermethrin, deltamethrin, etofenprox, lambdacyhalothrin, permethrin, mixture). This figure appears in color at www.ajtmh.org.
where IRS activities were sustained over 3 decades until the disease was eliminated. The possible adverse consequences of human exposure to DDT cannot be ignored, even with limited evidence, and merit further study. The risks to public health by deployment of DDT or other insecticides must be carefully weighed against the benefits, in this case the prevention of malaria.

The health and environmental effects of DDT when used exclusively for IRS are not known. The tendency is to compare DDT use in the 1950s and 1960s with that for IRS today. During the eradication period, DDT was the main tool for combating malaria. Approximately 40,000 tons of DDT were used annually during the malaria eradication period of 1955–1970, corresponding to only 15% of the global DDT production. The rest of the consumption was for agricultural pest control and domestic purposes. After the malaria eradication period, DDT use for public health purposes was about 30,000 tons per year during 1978–1982, and no major adverse health effects were reported in exposed populations. Nonetheless, possible soil and water contamination, effects on wildlife and the environment, and illicit use of DDT, particularly in agriculture, are real concerns. In India, DDT is known to be diverted for non-public health use and was banned as an agricultural pesticide in 1996. Since then no regulation has been put in place to ensure that DDT is used exclusively for disease vector control. Residues of DDT and its metabolites in human blood and the environment are detected even in areas where IRS is not implemented, suggesting diversion of DDT to agriculture. In contrast, a recent IRS program with DDT and pyrethroids in two mining towns in Zambia was conducted under the auspices of the Zambian Environmental Council in partnership with a private mining company. The challenge is to achieve such intersectoral and interagency cooperation at the national and regional levels to monitor the environmental impact of DDT when used exclusively for IRS.

**INSECTICIDE RESISTANCE: MONITORING AND MANAGEMENT**

The recent WHO position statement on IRS notes that the choice of insecticide must be informed by the following: (1) vector susceptibility to insecticides; (2) vector ecology and behavior; (3) toxicity and safety for humans and the environment, including contamination of agricultural goods; (4) efficacy and cost effectiveness compared with alternative insecticides; and (5) community acceptance. Although toxicity and safety concerns have made the use of DDT a contentious issue at the international level, the remaining factors (plus the burden of malaria) weigh heavily in the context of a national program.

Resistance to the insecticides used is a major operational concern in vector control efforts. Because monitoring efforts have been limited, the current spectrum of the insecticide resistance problem is not known in malaria endemic regions, particularly in Africa. Resistance to DDT was widespread in the early 1970s because of its intensive use in public health and agriculture and emerged after about 11 years of application. Although DDT has been used in limited quantities for disease vector control during the past 3 decades, there have been recent reports of resistance in malaria vectors from African countries. Pyrethroids and, to a lesser extent, organophosphates and carbamates are increasingly used for malaria vector control in endemic countries. Resistance monitoring, however, has concentrated mostly on pyrethroids because of the emphasis placed on ITNs for malaria prevention. Pyrethroid resistance is a major concern in western African countries and is a growing problem in eastern and southern African countries. The intensive use of pyrethroids for agricultural pest control is linked to the high levels of resistance observed in west African countries.

Research has shown 2 major mechanisms of resistance in mosquitoes: (1) increased metabolism of insecticides reducing the effective dose of insecticide available at the target site; and (2) reduced target site sensitivity leading to ineffective binding of a given dose of insecticide, also known as knockdown resistance (kdr). Each mechanism is complex; a diverse range of genes and enzyme families are involved in resistance development. Hence, malaria vectors may have multiple resistance mechanisms, which are field selected under insecticide selection pressure, and may be resistant to one or more classes of insecticides. For instance, kdr resistance,
which results from single point mutations in the genes that encode the voltage-gated sodium channel, is a common target site resistance mechanism in African malaria vectors that confers broad-spectrum resistance to pyrethroids and cross-resistance to DDT. Therefore, monitoring of kdr resistance is particularly important if ITNs and IRS with DDT are deployed simultaneously. On the other hand, resistance to pyrethroids can develop through a less tractable mechanism of metabolic resistance, which results from alterations in the levels or activities of insecticide-detoxifying enzymes. Although the absence of kdr resistance in a pyrethroid-resistant malaria vector may preserve susceptibility to DDT, the presence of metabolic resistance may confer cross-resistance to another class of insecticides, as recently reported for pyrethroid-resistant *A. funestus* with cross-resistance to the carbamate propoxur in South Africa and Mozambique. Intensive use of insecticides may also induce behavioral changes in malaria vectors, such as shifts in biting times and reduced resting periods, compromising vector control efforts.

The impact of detected resistance on the efficacy of insecticide-based vector control interventions highlights its operational significance. Several experimental hut trials in West Africa reported that ITNs reduced biting rates and caused mortality in local populations of *A. gambiae* in pyrethroid resistance areas. A field study from India revealed marked reductions in vector densities and malaria cases although the target malaria vector *A. culicifacies* was found to be resistant to DDT. On the other hand, pyrethroid resistance in *A. gambiae* interfered with the efficacy of IRS and led to a switch back to DDT in South Africa. The results of a study from Benin showed that ITNs and IRS with pyrethroids failed to control an *A. gambiae* population with a high level of kdr resistance genes. The results of this study stood in contrast with the results of several studies from Cote d'Ivoire that reported a continued efficacy of ITNs in areas with a comparable kdr resistance. Further molecular studies failed to explain the basis for differing contribution of kdr to pyrethroid resistance in *A. gambiae.*

Baseline assessment and routine monitoring of insecticide resistance in malaria vectors are crucial to inform vector control strategies. To protect the effectiveness of insecticides in use, it is important to detect the emergence of resistance at an early stage and monitor the impact on practical control and spread of resistance across the geographical range of malaria vectors through field studies with experimental huts. This monitoring and surveillance system is important for systematic data collection on vector species, vector behavior and ecology, and transmission patterns (i.e., entomological inoculation rates), which is currently not a routine practice in most endemic countries. This system can also serve as a platform to improve our understanding of the development of different resistance mechanisms and the potential for cross-resistance among insecticides—knowledge that is important in designing resistance management strategies. The rotation of insecticides is one of the proposed strategies that is currently under evaluation. However, an earlier modeling study showed that pre-planned rotation of insecticides did not provide any significant advantage over switching insecticides when resistance build-up was at an intolerable level. For effective action, susceptibility levels of primary malaria vectors to the various classes of insecticides should be closely monitored using standard bioassays. Much more important is the effect of resistance on malaria transmission as it relates to the effectiveness of interventions, as has been the case for pyrethroids and ITNs.

Such a program of insecticide resistance monitoring and surveillance will require training of a large number of competent program managers and technicians in classic and molecular entomology—a huge gap throughout tropical Africa as reported by the African Network on Vector Resistance (Figure 2)—and the establishment of a network of entomological surveillance sites with trained field staff. Underlying this challenge is the broader and urgent need to strengthen the managerial and operational capacity of national malaria control programs with human, technical, and financial resources.

### COSTS AND COST EFFECTIVENESS

In African countries and elsewhere where malaria is endemic, IRS is a highly cost-effective intervention (US $9–24 per disability-adjusted life year [DALY] averted). A recent study from Mozambique compared 2 operationally similar IRS programs implemented in a rural and a peri-urban area; the cost per person covered using carbamates was US $3.48 and US $2.16, respectively, and using alternative insecticides ranged between US $1.50–US $4.16 and US $0.74–US $2.70, respectively. The study reported that DDT had the lowest cost per person covered, followed by Icon® (lambda-cyhalothrin), Ficam® (bendiocarb), and propoxur. Table 4 presents the estimated costs of spraying DDT and other approved insecticides using the high end of the dosage range recommended by the WHO in consideration of application on mud surfaces. The estimations considered the duration of residual effect on mud surfaces for a period of 6 months, assuming an average of 200 m² sprayable surface per house. Water dispersable powders are used because of their low cost and longer residual activity on porous surfaces. The costs of insecticides (US $ per kg active ingredient) are based on the reports of 80 manufacturers in 20 different countries and do not include freight, import duties and taxes, and other external costs. Therefore, the reported costs of insecticides do not necessarily reflect the costs that may be incurred by the ministries of health in endemic countries. Such operational costs such as labor and transport are also not included in these estimations. These operational costs are highly variable across and within countries depending on the characteristics of the areas targeted for IRS, the insecticide of choice, and the spraying activity. The cost comparison results show that DDT is the least expensive insecticide; it costs $1.60 per house for 6 months at 2 g/m² and requires only 1 spraying round for that period. It is important to note that DDT has been successfully used in India at a target dose of 1 g/m² in areas where the major vector has shown resistance to this insecticide. With a marked reduction in the cost of deltamethrin from US $20 to US $4 per kg active ingredient in the recent past, the cost of this insecticide compares well with that of DDT, but deltamethrin requires 2 or more spraying rounds depending on the duration of the malaria transmission season, adding proportionately to the operational costs of IRS. The two insecticides are followed by malathion and lambda-cyhalothrin, which cost about 5 times more than DDT and require 3 and 2
spraying rounds, respectively, to achieve 6 months of residual activity. Bendiocarb and fenitrothion cost about 9 times more per house sprayed, and propoxur is the most expensive insecticide to provide 6 months of control.

In setting priorities for malaria control, a rule of thumb is to compare the cost effectiveness of IRS using DDT with that of using alternative insecticides and with that of other vector control interventions. Table 5 describes the advantages and disadvantages of key vector control interventions, including IRS, ITNs, and environmental management. Figure 3 shows the cost-effectiveness ratios of IRS (using DDT and lambda-cyhalothrin and considering 1 and 2 spraying rounds per year) and ITNs (considering nets with insecticide and insecticide only). A review of recent IRS and ITN projects concluded that the two interventions had comparable effectiveness, but the outcomes were not as impressive when compared with those of well-documented spraying projects of the 1950s–1970s. Increasing pyrethroid resistance may change these conclusions. Intervention effectiveness is locality specific; it is primarily a function of the extent of detected vector resistance interfering with practical control and the coverage rate

![Vector surveillance capacities in national malaria control programs (NMCP) and research institutions in 38 African countries. Product of the African Network on Vector Resistance: ANVR Newsletter Issue No 1, 2006.](image)

**Table 4**

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>Dosage (g/m²)</th>
<th>Approximate duration of residual effect on mud surfaces (months)</th>
<th>Number of spraying rounds per 6 months</th>
<th>Total dosage per 6 months (g/m²)</th>
<th>Formulation</th>
<th>Approximate amount of formulated product required per house (kg)</th>
<th>Approximate cost of formulated product (US$ per kg)</th>
<th>Cost per house (US$)</th>
<th>Cost ratio (DDT = 1)</th>
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<tbody>
<tr>
<td>DDT</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>75% WP</td>
<td>0.5</td>
<td>3.0</td>
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<td>1.0</td>
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<tr>
<td>Deltamethrin</td>
<td>0.025</td>
<td>3</td>
<td>2</td>
<td>0.05</td>
<td>2.5% WP</td>
<td>0.4</td>
<td>4.0</td>
<td>1.6</td>
<td>1.0</td>
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<tr>
<td>Malathion</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>6</td>
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<td>2.4</td>
<td>3.4</td>
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<td>5.1</td>
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<td>3</td>
<td>2</td>
<td>0.06</td>
<td>10% WP</td>
<td>0.1</td>
<td>72.0</td>
<td>8.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Bendiocarb</td>
<td>0.4</td>
<td>2</td>
<td>3</td>
<td>1.2</td>
<td>80% WP</td>
<td>0.3</td>
<td>46.0</td>
<td>13.8</td>
<td>8.6</td>
</tr>
<tr>
<td>Fenitrothion</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>40% WP</td>
<td>2.0</td>
<td>7.4</td>
<td>14.8</td>
<td>9.3</td>
</tr>
<tr>
<td>Propoxur</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>80% WP</td>
<td>1.0</td>
<td>18.8</td>
<td>18.8</td>
<td>11.8</td>
</tr>
</tbody>
</table>

*DDT, dichlorodiphenyltrichloroethane; WP, water-dispensable powder.*
achieved in the target community. Indeed, experience in the Solomon Islands showed that ITNs permitted a reduction in DDT spraying, but could not replace it without an increase in malaria incidence.\textsuperscript{80} It is also important to sustain interventions to realize their full potential. For these reasons and others, the studies comparing the cost effectiveness of IRS and ITNs have produced inconclusive results. In addition, it is unclear whether a combination of ITNs and IRS would be cost effective.

Few cost-effectiveness analyses of environmental management programs have been performed. One study of an integrated malaria control program in Zambia centering on environmental management showed that the initial costs per DALY averted were high because of setup costs, but the costs per DALY averted decreased substantially in the long term.\textsuperscript{81}

A central question in the debate on the role of DDT in IRS is its cost compared with that of alternative insecticides. It is important that the cost advantage of using DDT is well established when compared with alternatives. A number of recent studies have indicated that DDT is the least costly insecticide\textsuperscript{72,74} and that spraying programs with DDT are slightly cheaper than programs with other insecticides.\textsuperscript{72,82}

Absolute prices of insecticides for public health purposes are, however, difficult to assess because they do not reflect the true cost to a given country, including procurement, transportation, handling and disposal, freight, and other external costs.\textsuperscript{73,74}

Costs related to the availability and production of DDT is currently restricted to only a few manufacturers (i.e., in India, Ethiopia, and China\textsuperscript{24}). Presumably, WHO and other organizations will work toward making DDT and other insecticides available for IRS promptly, at low cost, and in a sustainable manner.

### Table 5

Advantages and disadvantages of key malaria vector control strategies\textsuperscript{4,5,6,7,5–7,64–76}

<table>
<thead>
<tr>
<th>Indoor residual spraying</th>
<th>Insecticide-treated nets</th>
<th>Environmental management†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>• Mosquitoes killed and repelled</td>
<td>• Mosquitoes killed and repelled</td>
<td>• Prevent mosquito maturation by eliminating breeding sites</td>
</tr>
<tr>
<td>• Community-wide protective effect</td>
<td>• Community-wide protective effect, if coverage rate is high, extended to neighboring communities\textsuperscript{15}</td>
<td>• Community-wide protective effect</td>
</tr>
<tr>
<td>• Once sprayed, no additional commitment from community</td>
<td>• Rebound effect not observed\textsuperscript{75}</td>
<td>• Useful in peri-urban and urban areas where transmission is focal\textsuperscript{7}</td>
</tr>
<tr>
<td>• Residual activity: 3–12 months, depending on the insecticide</td>
<td>• Individual and community decisions to use</td>
<td>• Useful in economic development sites where nonimmune populations may be concentrated</td>
</tr>
<tr>
<td>• Proven effectiveness in a variety of epidemiological settings</td>
<td>• Effectively treated nets with sizeable holes remain effective\textsuperscript{76}</td>
<td>• Sustainable reductions in transmission, morbidity, and mortality observed when integrated with other interventions\textsuperscript{70}</td>
</tr>
<tr>
<td>• No documented serious adverse effects on human health and the environment</td>
<td>• Proven effectiveness in a variety of epidemiological settings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No documented serious adverse effects on human health and the environment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Disadvantages</strong></th>
<th><strong>Disadvantages</strong></th>
<th><strong>Disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insecticide resistance monitoring and management</td>
<td>• Ineffective against exophagic malaria vectors</td>
<td>• Difficult to implement and maintain because of operational complexity (e.g., periodic maintenance, labor intensive)</td>
</tr>
<tr>
<td>• Ineffective against exophilic malaria vectors</td>
<td>• Decreased susceptibility and increasing resistance to pyrethroids, but nets may still be a practical means of personal protection\textsuperscript{83}</td>
<td>• Programs require technical capacity for implementation and vector surveillance</td>
</tr>
<tr>
<td>• Difficult to implement and maintain because of operational complexity (e.g., transportation into remote communities are difficult, labor intensive) and resource requirements</td>
<td>• Periodic net retreatment is required (as long-lasting nets become available, retreatment will cease to be a problem)</td>
<td>• High initial costs</td>
</tr>
<tr>
<td>• Programs require technical capacity for implementation and vector surveillance</td>
<td>• Distribution and sustainability problems, particularly in impoverished areas when nets are not distributed free of charge</td>
<td>• Intersectoral action is required</td>
</tr>
<tr>
<td>• Acceptability among community members</td>
<td>• Low coverage rates, particularly in high-risk groups such as children and pregnant women, when nets are not distributed free of charge</td>
<td>• Impact difficult to quantify when integrated with other interventions</td>
</tr>
<tr>
<td>• Required removal of all belongings, except large pieces of furniture, from the home</td>
<td>• Difficult to promote in areas of unstable transmission</td>
<td>• Some undesirable environmental impact if activities target wetlands</td>
</tr>
<tr>
<td>• Health and safety of sprayers and communities</td>
<td>• Individual attitudes and practices (e.g., ineffective for persons sleeping outside)</td>
<td></td>
</tr>
</tbody>
</table>

\* ITNs, insecticide-treated nets; IRS, indoor residual spraying.
† Environmental management encompasses draining and filling of breeding habitats, clearance of vegetation, and eliminating pools of stagnant water.
According to WHO, IRS can be effective in 89,90%
However, the program – which quickly
96% of the population the benefits of effective malaria control. In areas
In areas with unstable malaria transmission, IRS will prevent seasonal increases in transmission, will prevent and control epidemics, and can eliminate local transmission of malaria.
In areas with stable endemic malaria with moderately intense but seasonal transmission, IRS will prevent seasonal increases in transmission and reduce malaria prevalence and seasonal increases in morbidity and mortality.
In areas with stable hyperendemic malaria where transmission is intensely seasonal or perennial and without much seasonal flux, IRS will reduce malaria prevalence, incidence, morbidity, and mortality when applied more frequently than in the above instances.

Many malaria endemic countries have areas with the 2 or 3 levels of endemicity noted above and are loath to deny any population the benefits of effective malaria control. In areas where epidemics last only for a few months and do not return for years, promotion and provision of ITNs prove difficult, and the “fire brigade” approach with trained and equipped IRS spraymen seems to be the best precaution. Table 6 lists selected African countries that have successfully used DDT for IRS. In Madagascar, 7% of the population is at risk of epidemic malaria, especially in the central highlands. Disease had been controlled in this region during the 1950s through IRS with DDT, and the main malaria vector Anopheles funestus was nearly eradicated. However, the program’s emphasis on spraying decreased over time, An. funestus reappeared in large numbers, and a severe epidemic resulting in thousands of deaths occurred during 1985–1990 after a heavy rainfall. When DDT was reintroduced through a multi-intervention program, Opération de Pulvérisation Intra-Domiciliaire, by the government of Madagascar, the incidence of malaria was reduced greatly, albeit late.

A recent study assessed the impact of the Global Malaria Programe’s (formerly Roll Back Malaria) 5-year program in Eritrea, where 67% of the population lives in endemic areas. The study showed that the number of ITNs and the amount of insecticide used for IRS were both significantly correlated with a reduction in malaria morbidity.
Malaria had been controlled using IRS with DDT in Kwa-Zulu Natal, an epidemic-prone province in South Africa, from 1946–1995. During the malaria transmission season of 1991–1992, there were only 600 reported cases of malaria. However, because of growing environmental concerns and the presence of DDT in breast milk, South Africa substituted synthetic pyrethroids for DDT in 1996. An. funestus quickly reemerged (probably after entering from Mozambique) and were found to be resistant to pyrethroids without cross-resistance to DDT. From 1999–2000, 40,700 cases of malaria were reported. After DDT was reintroduced, the number of reported cases diminished rapidly, with 17,500 reported cases in 2001 and 3,500 reported cases in 2002.

Table 6 shows that in these 3 countries, IRS with DDT was not an isolated strategy. Treatment with antimalarial drugs, including artemisinin-based combination therapies (ACTs), and prevention were key components of the malaria control strategy in Madagascar, Eritrea, and South Africa. A comprehensive strategy must include multiple interventions and disease and vector surveillance, all of which require epidemiologic and entomological capacity within the national programs. Treatment of infected individuals may help to reduce transmission as ACTs have gametocytocidal properties. Evidence also suggests that successful vector control may help reduce drug resistance.
Successful IRS programs with DDT were previously implemented in Botswana, Namibia, Zimbabwe, and Mozambique. These countries are currently members of the southern African coalition of malaria endemic countries that embarked on a regional control program in the late 1990s.
Uganda, unlike the central highlands of Madagascar or the Kwa-Zulu Natal province of South Africa, is characterized by predominantly stable malaria transmission. This is one of the many countries considering deployment of DDT for IRS, and the situation illustrates the dilemmas faced by many countries. Proponents claim that given the financial resources required for spraying programs with deltamethrin, more households could be protected by using DDT. Opponents question the environmental and health impact of DDT. In addition, Ugandan and other government officials are rightfully concerned that if DDT is reintroduced, trade relations with the European Union (EU) may be endangered. In 2005, the EU warned Uganda that if DDT were used for malaria control, stringent measures would have to be taken to ensure that foodstuffs were not contaminated. Even with precautions, a negative perception of Ugandan agricultural products may have profound economic consequences. Before implementing an IRS program with DDT in these countries, potential barriers to trade must be thoroughly addressed.

IMPLEMENTATION, MONITORING, AND EVALUATION

Recommendations for IRS with DDT must be evidence-based and consider epidemiologic and entomologic, operational, and economic factors (Table 7). The effectiveness of IRS has been demonstrated in both unstable, epidemic-prone...
areas and stable, endemic areas of southern Africa.\textsuperscript{21,30,49} In areas of high and moderate transmission, ITNs provide another means of malaria control, and decisions about which of the 2 interventions is preferable will depend on operational feasibility and resource availability.\textsuperscript{90,99} Most importantly, the two interventions are not mutually exclusive and their implementation depends upon local conditions, population acceptability, costs, sustainability, technical expertise, monitoring and evaluation, and national policies.

Operational issues pose a significant barrier to successful implementation and were major impediments to the success of national eradication programs in the 1950s and 1960s. These operational issues involve access to an adequate supply and distribution of quality DDT (when stocks being exported or donated and when old stocks being used), capacity to effectively plan and manage IRS programs, and ability to assess the potential impact of a spraying program through monitoring of effective forms of resistance, malaria disease surveillance, and evaluation of any adverse effects of DDT to human health and the environment. Countries should specify how they intend to provide supervision on decentralized activities and train sprayers and raise awareness among spraying personnel and targeted communities on issues relating to DDT use. The acute toxicity of DDT to human’s is low and is not a major concern. The stigma associated with IRS may be difficult to overcome in general and communities may not tolerate the often visible residues left by the insecticide on the wall. It is critical that countries have a plan for storage and disposal of insecticides and are committed to preventing the diversion of DDT into agriculture. Lastly, the ability to detect the emergence and spread of vector resistance to DDT of a kind that has practical impact on intervention effectiveness and the susceptibility levels to alternative insecticides are key in effective management of insecticide resistance and sustainability of IRS activities.

Monitoring and evaluation are crucial to assess the success of any malaria control program. Monitoring serves to measure outcomes and to assess the effectiveness of interventions. Several approaches for data collection on malaria outcomes should be considered. Data from national health information systems, collected from health facilities, can provide information on cases of severe malaria and case fatality rates. However, such data represent only those facilities that regularly report cases and measure morbidity and mortality only in

<table>
<thead>
<tr>
<th>Place</th>
<th>Context</th>
<th>Date</th>
<th>Control measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madagascar Highlands</td>
<td>• History of epidemic malaria in the highlands since the 1800s&lt;br&gt; • Weakening malaria control efforts</td>
<td>1949–1960 Post-1960</td>
<td>• IRS with DDT and chloroquine treatment of infected individuals\textsuperscript{56}&lt;br&gt; • Spraying with DDT limited to 3 feet; closure of treatment centers\textsuperscript{86}&lt;br&gt; • 1996: Establishment of malaria surveillance system to record malaria cases at the 536 health centers in the region\textsuperscript{87}</td>
<td>• 1954: disappearance of Anopheles funestus; eradication nearly achieved in 1969\textsuperscript{93}&lt;br&gt; • 1980: 3-fold increase in the number of malaria cases\textsuperscript{86}&lt;br&gt; • Reappearance of An. funestus in mid-1970s\textsuperscript{84}&lt;br&gt; • Severe epidemic (1985–1990) with 40,000 deaths\textsuperscript{84}&lt;br&gt; • 28% decrease in the incidence of malaria in sprayed areas only, with no change in incidence in unsprayed areas\textsuperscript{87}&lt;br&gt; • 0.8% and 4.5% prevalence of malaria parasites in schoolchildren in sprayed and unsprayed areas, respectively, at 1,000–1,500 m\textsuperscript{86}&lt;br&gt; • Prevalence of Plasmodium positive schoolchildren was 23.8% and 0.4% before and after OPID, respectively, at 1,000–1,500 m\textsuperscript{86}&lt;br&gt; • Significant negative correlation between the number of ITNs distributed and the amount of DDT/malathion used for IRS with malaria morbidity&lt;br&gt; • No additional benefit from IRS when added to ITN vector control\textsuperscript{84}&lt;br&gt; • 600 reported cases of malaria in the province in 1991–1992\textsuperscript{89}&lt;br&gt; • 1998–1999: reinvasion of An. funestus and doubling of malaria cases\textsuperscript{86}&lt;br&gt; • 2000: 40,700 reported cases of malaria\textsuperscript{84}&lt;br&gt; • About 90% reduction of malaria cases after reintroduction (2000–2004) compared with before (1996–1999)\textsuperscript{90}&lt;br&gt; • 2001: 17,500 reported cases; 2002: 3,500 reported cases\textsuperscript{90}</td>
</tr>
<tr>
<td>Eritrea</td>
<td>• Implementation of a 5-year malaria control program</td>
<td>2000–2004</td>
<td>• ITNs&lt;br&gt; • IRS with DDT&lt;br&gt; • IRS with malathion&lt;br&gt; • Improved patient management&lt;br&gt; • Antimalarial drugs&lt;br&gt; • Environment controls</td>
<td>• 1954: disappearance of Anopheles funestus; eradication nearly achieved in 1969\textsuperscript{93}&lt;br&gt; • 1980: 3-fold increase in the number of malaria cases\textsuperscript{86}&lt;br&gt; • Reappearance of An. funestus in mid-1970s\textsuperscript{84}&lt;br&gt; • Severe epidemic (1985–1990) with 40,000 deaths\textsuperscript{84}&lt;br&gt; • 28% decrease in the incidence of malaria in sprayed areas only, with no change in incidence in unsprayed areas\textsuperscript{87}&lt;br&gt; • 0.8% and 4.5% prevalence of malaria parasites in schoolchildren in sprayed and unsprayed areas, respectively, at 1,000–1,500 m\textsuperscript{86}&lt;br&gt; • Prevalence of Plasmodium positive schoolchildren was 23.8% and 0.4% before and after OPID, respectively, at 1,000–1,500 m\textsuperscript{86}&lt;br&gt; • Significant negative correlation between the number of ITNs distributed and the amount of DDT/malathion used for IRS with malaria morbidity&lt;br&gt; • No additional benefit from IRS when added to ITN vector control\textsuperscript{84}&lt;br&gt; • 600 reported cases of malaria in the province in 1991–1992\textsuperscript{89}&lt;br&gt; • 1998–1999: reinvasion of An. funestus and doubling of malaria cases\textsuperscript{86}&lt;br&gt; • 2000: 40,700 reported cases of malaria\textsuperscript{84}&lt;br&gt; • About 90% reduction of malaria cases after reintroduction (2000–2004) compared with before (1996–1999)\textsuperscript{90}&lt;br&gt; • 2001: 17,500 reported cases; 2002: 3,500 reported cases\textsuperscript{90}</td>
</tr>
<tr>
<td>South Africa: KwaZulu-Natal</td>
<td>• Long history of malaria control with IRS&lt;br&gt; • Concerns about the environmental effects of DDT and about DDT found in breast milk&lt;br&gt; • Identification of pyrethroid-resistant An. funestus</td>
<td>1946–1996 1996–1999 2000</td>
<td>• IRS with DDT began in 1946 with complete coverage of malarial regions by 1958\textsuperscript{21}&lt;br&gt; • 1996: Synthetic pyrethroids were substituted for DDT\textsuperscript{21}&lt;br&gt; • Reintroduction of DDT\textsuperscript{21}&lt;br&gt; • 2001: Artemether-lumefantrine became first-line therapy for uncomplicated malaria\textsuperscript{92}</td>
<td>• 1954: disappearance of Anopheles funestus; eradication nearly achieved in 1969\textsuperscript{93}&lt;br&gt; • 1980: 3-fold increase in the number of malaria cases\textsuperscript{86}&lt;br&gt; • Reappearance of An. funestus in mid-1970s\textsuperscript{84}&lt;br&gt; • Severe epidemic (1985–1990) with 40,000 deaths\textsuperscript{84}&lt;br&gt; • 28% decrease in the incidence of malaria in sprayed areas only, with no change in incidence in unsprayed areas\textsuperscript{87}&lt;br&gt; • 0.8% and 4.5% prevalence of malaria parasites in schoolchildren in sprayed and unsprayed areas, respectively, at 1,000–1,500 m\textsuperscript{86}&lt;br&gt; • Prevalence of Plasmodium positive schoolchildren was 23.8% and 0.4% before and after OPID, respectively, at 1,000–1,500 m\textsuperscript{86}&lt;br&gt; • Significant negative correlation between the number of ITNs distributed and the amount of DDT/malathion used for IRS with malaria morbidity&lt;br&gt; • No additional benefit from IRS when added to ITN vector control\textsuperscript{84}&lt;br&gt; • 600 reported cases of malaria in the province in 1991–1992\textsuperscript{89}&lt;br&gt; • 1998–1999: reinvasion of An. funestus and doubling of malaria cases\textsuperscript{86}&lt;br&gt; • 2000: 40,700 reported cases of malaria\textsuperscript{84}&lt;br&gt; • About 90% reduction of malaria cases after reintroduction (2000–2004) compared with before (1996–1999)\textsuperscript{90}&lt;br&gt; • 2001: 17,500 reported cases; 2002: 3,500 reported cases\textsuperscript{90}</td>
</tr>
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those who access health services. Thus, local community and household surveys, such as Demographic and Health Surveys (http://www.measuredhs.com/) and the Malaria Indicator Survey (https://www.rbm.org.int/merg), can supply information not provided by health information systems. These surveys are useful for collecting data on all-cause under-5 mortality, use of interventions such as ITNs, and use of antimalarial therapies.6

In addition to disease monitoring, efforts must be made to assess human and environmental exposure. Levels of DDT are used as markers of exposure and have been measured in blood, breast milk, dust, soil, water, sediment, and fish. Methods for extraction and identification of DDT from these media with gas chromatography-mass spectroscopy have been developed. Studies of human exposure have assessed DDT levels in blood and breast milk. In Mexico, studies have shown that blood levels of DDT and DDE in women living in areas that were heavily sprayed are higher than in areas where less DDT had been used. In all study areas, sprayers had the highest levels of exposure. A reduction in blood levels of DDT and DDE in the exposed population was noted over 2 years after the cessation of spraying programs. Breast milk containing DDT has been identified in women throughout the world, including Swaziland and South Africa.

Continued monitoring of DDT levels in breast milk is important to ensure that the acceptable daily intake for infants is not exceeded and to assess its clinical importance.

Studies of environmental exposure are also important for assessing the potential impact of DDT on ecosystems. Concentrations of DDT and its metabolites in indoor and outdoor soils were significantly higher in areas more highly exposed to DDT than in less exposed areas in Mexico. In China, DDT has been identified in soil, sediment, and wildlife; concentrations in birds were greater than those in fish, suggesting bioaccumulation of DDT. Similar studies assessing contamination of environmental media have been conducted in Brazil and KwaZulu-Natal, South Africa, where DDT was identified in the water, particularly attached to sediment particles. Analyses of DDT in humans and the environment should include measurements of DDT and its main metabolites, DDE and dichlorodiphenyldichloroethane (DDD). Before the implementation of spraying programs, baseline assessments should be conducted so as to establish any impact of IRS with DDT on human health and the environment.

Article 11 of the Stockholm Convention calls for “research, development, monitoring and cooperation pertaining to persistent organic pollutants (POPs),” including their “presence, levels, and trends in humans and the environment” as well as “effects on human health and the environment.” However, for many developing nations, this will require an overall strengthening of their scientific and technical capacity. To establish research and monitoring for the health and environmental effects of DDT, as described in the studies above, it will require training on laboratory protocols and safety, procurement of necessary equipment, and establishment of databases. The UNEP has already established a Global POPs Monitoring Program to evaluate the effectiveness of the Stockholm Convention. With the recent endorsement of IRS with DDT by the WHO, the work of the Monitoring Program and of existing laboratories with the capacity to monitor POPs will become important in training and capacity building in developing countries.

### RESEARCH NEEDS

The use of IRS with DDT has proven effective in controlling malaria transmission in areas where malaria vectors were susceptible or showed some degree of resistance as indicated by high frequency of resistance genes and where governments could properly manage such programs with high spray coverage and proper supervision. Several important research questions remain concerning the safety and efficacy of IRS with DDT. Adverse health effects of DDT when used exclusively for IRS have not so far been demonstrated. Prospective cohort studies linking exposure data (as described above) to health outcomes should be conducted. Efforts should also be made to accurately record the amounts of DDT used for IRS. Such data will help to correlate DDT exposure with health and environmental outcomes. Research should focus on the effects of exposure on children in areas where DDT is being used and on the development of new methods for improved monitoring of DDT in various environmental settings.
The development and spread of insecticide resistance are dependent on the volume and frequency of application of insecticides and the inherent characteristics of the malaria vectors against which they are used.\textsuperscript{11} All WHO-recommended insecticides for IRS, with the exception of DDT, are widely used in agriculture today. A detailed understanding is needed of the role of agricultural as well as domestic use of insecticides in the development of resistance. Knowledge of the genetic structure and dispersal patterns of malaria vectors is important for predicting the spatial and temporal spread of resistance through gene flow between vector populations.\textsuperscript{61} Yet only field studies of mosquito populations can facilitate timely operational responses and a better understanding of the impact of different resistance mechanisms on the effectiveness of IRS. Further research on the molecular basis of insecticide resistance is needed for the development of new and safe insecticides.\textsuperscript{110} The question of who will finance and develop such insecticides warrants further discussion.

The cost effectiveness of various vector control methods is important to policy makers when trying to decide how to allocate resources among competing interventions. In areas with high and moderate transmission, ITNs have proved equally effective\textsuperscript{111} and have been promoted, whereas IRS has been used mainly to control unstable, epidemic malaria. The use of IRS with DDT must be studied under different epidemiologic settings (rural versus urban, high and low endemic versus epidemic transmission) to understand where and how it is most cost effective. Another important question to policy makers when trying to develop a multi-component malaria control strategy is estimating the additional benefits of introducing IRS in an area where ITNs are widely used. Lastly, behavioral research on local attitudes and practices and the social acceptability of IRS is exceedingly important before and during the time such interventions are deployed on a large scale in a given area.

**DISCUSSION**

The low-cost insecticide DDT remains effective against malaria vectors in Africa. The possible adverse health and environmental effects of DDT exposure through IRS are not known and pose a real concern. Less persistent insecticides that do not bioaccumulate in adipose tissue would be preferable. However, the development of new insecticides for public health has been slow. Less than 10% of the insecticides developed since the 1970s have been considered for malaria vector control through IRS.\textsuperscript{112} The reality is that all insecticides used in public health are initially developed for the agriculture market, and it is unlikely that pesticide companies decide to invest in research and development of insecticides exclusively for disease vector control. Pesticide companies must be given incentives for developing new insecticides. Public–private partnerships between drug companies and public agencies have been successful in spurring research and development and providing new drugs to those in developing nations at a low cost (e.g., the Malaria Medicines for Malaria Venture and the Drugs for Neglected Diseases Initiative). Similar partnerships may reduce the cost of developing and registering new insecticides and may foster an interest among pesticide companies in expanding their research to include public health insecticides. In this respect, the efforts of the Innovative Vector control Consortium are laudable.\textsuperscript{113} However, for this to occur, international agencies must recognize the importance of IRS and other transmission control interventions in integrated vector control as complementary strategies to increase the effectiveness of control efforts. The renewed position of WHO on IRS is a major step toward this direction. Tiered pricing, which has been used to provide vaccines and antiretroviral drugs for HIV/AIDS to those who are in need in developing countries, may also apply to public health insecticides. With tiered pricing, developed nations are charged higher prices as a way to recoup losses accrued by charging less to poorer nations. In a similar way, pesticide companies might charge lower prices to non-profit organizations and governments who intend to use the insecticide for malaria control while maintaining higher prices for insecticide purchases for agricultural use.

Critics fear that DDT will once again cause widespread environmental damage. There is also a risk of adverse effects of DDT and its metabolites to human health. However, the amount of DDT used in public health does not compare with the quantities used in agriculture prior to its ban for this purpose in developed countries. Furthermore, DDT is recommended for spraying indoors today whereas previous public health application of the insecticide before its detrimental environmental effects were observed in the early 1960s included aerial spraying of large areas in the United Sates and other developed countries, primarily focusing on marshes and swamps and adjacent water bodies.\textsuperscript{114} With proper regulation and management of the use of DDT in the public health sector, its illicit use in agriculture and the potential adverse effects on human health and the environment can be minimized. Under the Stockholm Convention, the use of DDT for disease vector control is monitored through records of which nations are using DDT and in what quantities. These national records may provide a useful tool for the monitoring of annual DDT production and ensure that only the amount of DDT that is needed for malaria control is produced each year.

The WHO reports that DDT is the insecticide of choice for malaria vector control in 10 endemic countries, and many others are considering its deployment. According to the DDT register established under the Stockholm Convention, China, Ethiopia, and India are the only countries where DDT is being produced today. Interest will increase greatly in its availability. DDT will need to be imported. Procurement costs and maintenance of adequate supplies will be a major issue in endemic countries as observed for other key antimalarial commodities, such as ACTs and ITNs.

African countries have implemented effective IRS programs with DDT and other insecticides. The reconsideration of IRS with DDT today is primarily driven by the relative cheapness of DDT compared with alternative insecticides for IRS. The ineffectiveness of current control strategies has been another strong motive. There is now global support to scaling up net coverage in vulnerable groups, particularly through maternal and child health programs, and the expectation is that more than half a million child deaths will be averted with the distribution of long-lasting insecticidal nets. Each country should investigate whether IRS would be a cost-effective strategy for malaria control after considering the intervention efforts already in place, the localized dynamics of malaria transmission in target areas, and the existing op-
erational capacity. Training of program managers and technicians in entomology and proper supervision of field staff during spraying operations, along with routine entomological and disease surveillance, is key in effective implementation. From an operational point of view, IRS with DDT will eventually lead to decreased sensitivity and resistance in malaria vectors. However it should be noted that DDT resistance was not detected in South Africa from 1946–1995. This is probably because strict measures were taken to prevent its diversion to agriculture where Anopheles larvae could develop resistance if under selection pressure. To ensure sustainability in IRS activities, the use of alternative insecticides to DDT and methods to use them must be the focus of the research agenda on integrated vector control.

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Authors’ addresses: Shobha Sadasivaiah, Weill Cornell Medical College of Cornell University, 1300 York Avenue, New York, NY, 10021-5320, Tel: 301-496-0815, Fax: 301-496-8496, E-mail: sshobha@med.cornell.edu. Yezim Tozan, Earth Institute, Columbia University, B15 Hogan Hall, Mail Code 3277, 2910 Broadway, New York, NY 10025-7822 and Disease Control Priorities Project, Fogarty International Center, National Institutes of Health; Pierre Guillet, Global Malaria Programme, WHO; and Robert Novak and Uriel Kitron, University of Illinois at Urbana Champaign for their guidance and feedback. The views expressed in this article do not necessarily reflect the views of those listed above.

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