

Scientific and Technical Advisory Panel



The Scientific and Technical Advisory Panel, administered by UNEP, advises the Global Environment Facility (Version 5)

STAP Scientific and Technical screening of the Project Identification Form (PIF)

Date of screening: 27 February 2008

Screener: Douglas Taylor, STAP Secretary

PIF primary review by:

Prof. Chris Curtis (London Sch of Hygiene & Trop. Med.)

Panel member validation by: John Buccini (Consultant)

I. PIF Information

GEFSEC PROJECT ID: 3648

GEF AGENCY PROJECT ID:

COUNTRY(IES): Global

PROJECT TITLE: DSSA Demonstrating and Scaling-up of Sustainable Alternatives to DDT in Vector Management (Program)

GEF AGENCY(IES): UNEP (IA)

OTHER EXECUTING PARTNERS: WHO

GEF FOCAL AREA (S): Persistent Organic Pollutants,

GEF-4 STRATEGIC PROGRAM(S):

NAME OF PARENT PROGRAM/UMBRELLA PROJECT: DSSA Demonstrating and Scaling-up of Sustainable Alternatives to DDT in Vector Management (Program)

Full size project GEF Trust Fund

II. STAP Advisory Response

1. Based on this PIF screening, STAP's advisory response to the GEF Secretariat and GEF Agency(ies):
Minor revision required

III. Further guidance from STAP

While in general supporting the objectives of the proposed program, STAP suggests that it is very important that any decisions to replace Indoor Residual Spraying (IRS) with DDT by other methods of malaria vector control, or to continue or commence the use IRS with DDT, are based primarily on scientific evidence. It is remarkable how little reliable comparative data exist despite years of polemics about DDT. It is suggested that a major feature of the proposed program should be a series of multi-armed trials using DDT versus using various alternatives. The relative effectiveness of various methods of vector control presumably depends on features of the local *Anopheles* species, such as their tendency to rest indoors, their time of biting and tendency to bite humans rather than animals, their susceptibility or resistance to DDT and alternative insecticides and the feasibility of finding and treating all breeding sites within mosquito flight range of the villages which it is intended to protect. Also of great importance are the willingness of the local people to support and participate in the control operations and the effectiveness of efforts to explain to the people why these operations are to be conducted in the ways proposed and that at the end of a 3 year trial everyone would benefit by being provided with the method which has been found best.

The following screening report applies to the submitted PIF for the program, but is also relevant to the separately submitted PIFs on regional actions.

The existing PIF for the program is very vague about what the proposed projects will actually do. In making more explicit plans the following points should be borne in mind:-

1. Longnecker (2001, Lancet 358: 110-4) reported an association of DDT residues in serum samples from U.S. women (samples stored frozen since the 1950s-60s) with history of pre-term births, which would presumably lead to a lowering of maternal and infant health. However, Giglioli (1972, Bull Wld Hlth Org 46: 181) reported on maternal and infant health in Guyana in the 1930s, before introduction of DDT, in the 1940s when DDT was intensively used for IRS and the 1950s after it had, temporarily, eradicated malaria. The health indices improved progressively over these three decades, strongly suggesting that any harm associated with DDT residues was far outweighed by the benefits of malaria eradication. Updated studies of this kind (over a shorter time scale than whole decades) are urgently needed as part of trials in which IRS with DDT is compared with other methods of malaria vector control.

2. Use of DDT for IRS is cheaper per house protected per year than use of a pyrethroid for this purpose (Walker, 2000, *Med Vet Entomol.* 14:345). In Africa the cost difference is not very great, but greater differences are reported from India where DDT is manufactured for local use. Any comparative trials of different control methods should attempt to estimate likely overall costs of each method when used routinely. It should be noted that where health budgets are severely restricted, a cheaper method would allow more communities to be protected.
3. DDT has a stronger tendency to drive mosquitoes out of houses (or prevent their entry) than does a pyrethroid, which tends to kill mosquitoes more quickly in the absence of pyrethroid resistance (Grieco et al, 2007 *PLoS* 8: 716). Because of this excito-repellency effect, in monitoring the effect of indoor use of insecticides it is important to use exit traps on windows in conjunction with collections in light traps set beside occupied bednets (Lines et al (1991, *Bull Ent Res* 81: 77) and collections of indoor resting mosquitoes. Human landing catches for monitoring malaria vector populations ought to be considered obsolete (except for monitoring effects of repellents applied to skin) because human landing catches expose people to extra malaria risk and are a very wasteful use of the time of field teams.
4. The Stockholm Convention contains an amendment introduced by the South African delegation at the final round of negotiations in 2000 and agreed *nem.con.* by all 150 national delegations. This emphasises the difference between outdoor agricultural use of DDT which may lead to entry of DDT derivatives into the food chain and IRS where appreciable ecological effects are unlikely. The amendment concurs with the banning of outdoor agricultural use of DDT but specifically authorises careful use of IRS with DDT against vectors.
5. South Africa had successfully used IRS with DDT against malaria vectors for 50 years. In the 1980s a comparative trial in experimental huts suggested better performance of IRS with a pyrethroid insecticide than with DDT (LeSeuer & Sharp, 1993, *J.Amer Mosq Contr Assoc.*). In 1995 there was a switch to IRS with a pyrethroid. Within 4 years the number of malaria cases had increased 4x and *Anopheles funestus* were found which had evolved resistance to pyrethroids but not DDT (Hargreaves et al, 2000 *Med Vet Ent* 14: 181), There was a switch back to DDT in 2001 and in the next two years malaria cases declined by 91% (Maharaj et al, 2005 *S.Af Med J* 95: 871).
6. In Central Asia and the southern Caucasus malaria was almost eliminated under the former Soviet Union by IRS with DDT combined with use of larvivorous fish to control *Anopheles* larvae and intensive use of anti-malarial drugs to prevent human infections persisting and producing *Plasmodium* gametocytes which could infect mosquitoes. With the decline of the universally available health service and of anti-mosquito campaigns after the end of the Soviet Union there was resurgence of malaria but obtaining reliable data on the present situation appears to be difficult. This is presumably the reason for contradictory statements in the PIF about the proposed project in these countries which on the one hand states that "in general, malaria cases are reduced" and "several countries are experiencing resurgence of vector borne diseases, mainly malaria". Former Soviet stocks of DDT are reported to still exist and may be being illegally sold for agricultural use. Clearly greater efforts should be made to ban this. In the PIF there are frequent mentions of collecting and destroying these stocks, but also one mention of "reverting back to formal use of (relatively cheap) DDT for malaria control as allowed under the Stockholm Convention". Before this is done, standard WHO tests should be applied for quality (especially suspensibility) of these stocks. The *Anopheles* malaria vectors found by P.Marchant working in Tajikistan are *An.superpictus*, *An.pulcherrimus* and *An.hyrchanus*.
7. In India much more DDT is used than in all of the rest of the world. Malaria incidence was reduced by about 99.8% by use of IRS with DDT in the 1950s-60s. More recently there has been a partial resurgence. This is commonly blamed on evolution of resistance to DDT and some other insecticides in some areas. However, this resistance only affects *An.culicifacies* and *An.stephensi* and not other important vectors such as *An.fluviatilis*. There is also a major problem in sustaining coverage with IRS in a high percentage of the houses in villages. Sharma et al (2005 *J.Vect Borne Dis* 42: 54) showed that where conventional tests show a high level of DDT resistance in *An.culicifacies*, if high % house coverage is ensured, major impact on mosquitoes and malaria can still be achieved. This emphasises the need to follow up laboratory detection of resistance genes with field studies of the extent to which they affect practical control. Recently, in Karnataka state, Ghosh et al (2005 *Trans Roy Soc Trop Med Hyg* 90: 101) have reported remarkable reductions in malaria by introduction of larvivorous fish into all ponds and wells in villages with checking and re-stocking, where necessary, every 6 months.
8. In the 1950s-60s IRS with DDT plus concerted use of chloroquine for human treatment greatly reduced malaria prevalence in Zanzibar. Resistance to DDT but not pyrethroids was detected in *An.gambiae* from Zanzibar the 1970s. A campaign using DDT in the 1980s failed, presumably due to the DDT resistance. In the last three years improved malaria diagnosis, widespread provision of Insecticide Treated Nets (ITNs) , IRS with a pyrethroid and use of Artemisinin Combination Therapy has reduced malaria in Zanzibar almost to the point of elimination.

9. Trials in Tanzanian villages showed that community-wide provision of ITNs or IRS with DDT reduced mosquito survival and hence percentage infective with *Plasmodium* sporozoites (Magesa et al, 1991, Acta Trop 49: 97), i.e. ITNs, when used community-wide, are not just a means of personal protection but reduce the infective mosquito population, as does IRS. Further multi-village trials compared IRS and ITNs using the same pyrethroid (lambda-cyhalothrin) for both purposes in each of four villages. Before starting the interventions a year of data on the vector populations and on malaria incidence and prevalence were collected to confirm comparability of the villages. After intervention Curtis et al (1998, Trop Med Int Hlth 3: 619-631) reported very similar impact of IRS and ITNs on the infective vector population, the numbers fed on human blood and prevalence and incidence of malaria. Maxwell et al (2003 Mal J 2: 28) used similar methodology to compare the percentage impact of ITNs on vectors and the disease in lowland and highland areas in Tanzania where the initial intensity of transmission was 15x greater in the lowlands than the highlands.
10. Where malaria transmission is intense and the disease is highly endemic the proportion of mosquitoes infective with *Plasmodium* sporozoites is measurable by enzyme linked immunosorbent assay (ELISA, Burkot et al, 1984, Amer J Trop Med Hyg 33: 783) and people develop considerable levels of immunity as a result of repeated malaria attacks. In such cases the successful application of IRS or ITNs is demonstrable by statistically significant reduction of the % of mosquitoes with sporozoites on sample sizes of a few hundred captured mosquitoes. However, many humans carry low level *Plasmodium* infection without symptoms and the cases which cause symptoms and may cause death are those with high parasite densities resulting in fever and anaemia. Thus in such areas blood samples of patients with fever need to be quantified for parasite and haemoglobin density.
The situation is different in areas with less intense malaria transmission and consequently little or no development of immunity. In such areas measurement of the proportion of mosquitoes with sporozoites with acceptable accuracy would require unfeasibly large sample sizes. Thus it is better to devote efforts to mosquito dissection and observing them for the proportion parous, which is a measure of mean mosquito survival which should be much reduced if IRS or ITNs are performing well. Also in such areas almost any *Plasmodium* infection is likely to lead to fever. Thus use on fever patients of Rapid Diagnostic Kits, which give a non-quantitative positive or negative answer, will distinguish fevers associated with malaria infection from those due to other causes. Use of these kits should allow avoidance of the strong tendency of medical staff to "over-diagnose" malaria and attribute all fevers to this cause.
11. By intensive use of the bacterial toxin Bti which is specifically lethal to mosquito larvae, Fillinger & Lindsay (2006, Trop Med Int Hlth 11: 1) reported a major impact on the *An.gambiae* population in a Kenyan town. However because of the short persistence of Bti checking, and if necessary re-treatment of hundreds of potential breeding sites, was required every week. By contrast, using the juvenile hormone mimic pyriproxyfen applied to rainwater-filled gem pits and river bed pools in Sri Lanka, Yapabandara et al (2004, J.Amer Mosq Contr Assoc 20: 395) reported that re-treatment only about three times a year was necessary to prevent any emergence of adult *Anopheles* from all the pits in villages. Major impacts were thereby achieved on the prevalence of malaria infection and the incidence of malaria fever cases.
12. Some *Anopheles* malaria vectors bite out of doors before people go to bed. In such cases it seems likely that IRS or ITNs will not be effective in controlling malaria. In Bolivia, against an *An.darlingi* population which bit early in the evening, Hill et al (2007, Brit Med J 335: 1023) reported a strong impact on malaria incidence by concerted community-wide use of a mosquito repellent (p-menthane diol derived from lemon eucalyptus). It is important to emphasise the need for community-wide use of a repellent which is not an insecticide, otherwise use of repellent by some people will result in diversion of mosquitoes to non-users and little or no overall benefit on malaria incidence in the community.

Taking into account the above points, UNEP and WHO may wish to consider a series of trials, in areas representative of each of the main biological settings in which malaria is transmitted, to assess the impact, on the malaria vector populations and on human health, of IRS with DDT compared with the most promising alternative methods of malaria vector control. These trials should be planned in close consultation with local experts on mosquitoes and malaria and the following outline protocol may be modified with their advice. Each of the interventions should be replicated in at least four separate villages and there should be a set of villages without any intervention until the end of the trial. Data should be collected in all the villages for a year before introducing any of the interventions to check on the comparability of the mosquito populations and human health in the villages. Then each intervention should be randomly assigned to four of the villages. In the statistical analysis of the data account should be taken of the "clustering" effect of each of the interventions being applied in (as far as possible) all of the houses in one set of four of the villages and the other interventions being tested in all the houses in others of the villages.

The inhabitants and leaders of the villages should be fully informed well in advance of the plans and given a chance to choose to refuse to participate. It should be explained that, at the end of the first year, four of the villages would be publicly allotted at random to receive no anti-mosquito intervention until the end of the trial, but it should be explained that health surveys with appropriate treatments will be provided in these villages as in all the others.

Appropriately trained local residents should be appointed in each village to carry out a full census and keep a continuous check on the health of pregnant women and young children, live and still births and deaths of all age groups. In addition members of the research team should visit each village once a month to examine 100 people randomly picked from the census list and record fevers and take blood samples for examination for malaria by trained microscopists or with Rapid Diagnostic Kits (see item 10 above) and to test for anaemia.

An entomological team should visit eight pre-selected “sentinel” houses in each village once a month to set light traps beside bednets to run overnight in four of the houses and to set exit traps on the windows of the other four and to collect from them resting mosquitoes in the bedrooms and to observe what proportion were bloodfed. The mosquitoes would be tested for presence of *Plasmodium* sporozoites or dissected and scored for parity depending on the intensity of malaria transmission in the area (see item 10 above).

It is suggested that the interventions to be tested in comparison with IRS with DDT may include IRS with a pyrethroid, ITNs, larval control with pyriproxyfen or larvivorous fish and community-wide application of repellent to the skin in the evening in areas where biting is at that time and not in the middle of the night. It is suggested that three items are selected from this list, depending on the behaviour of the local vector populations and on the results of tests for DDT and pyrethroid resistance, backed up by field studies of whether any laboratory detected resistance actually interferes with practical use of insecticides. Thus, including the four villages for testing IRS with DDT and the four control villages, a total of 20 villages would be needed for the proposed study of single interventions. It is proposed that this study should last one year. The idea of multiple interventions is frequently proposed. It is suggested that when the results of the one year study of single interventions are available, the two best should be combined in the same villages and this double intervention should be tested in comparison with villages continuing to use these two interventions singly. The aim would be to determine to what extent the two interventions together synergise each other. When this year’s study is complete all villages (especially those which acted as controls) would be offered at least five years provision of the best of the interventions. During the trial a careful check should be kept on the costs of applying each of the interventions, but excluding the costs only incurred to collect research data. The aim would be to make realistic estimates of the costs of routine use of each of the interventions.

The final outcome of the trial, occupying a total of three years, should be convincing evidence on which to decide whether IRS with DDT should or should not be replaced, based on effectiveness in controlling vectors and malaria, cost and whether IRS with DDT, or any of the other interventions cause harm or benefit to maternal and child health.

Roughly in line with the geographical areas outlined in the Annexes of the existing document comparative trials are proposed in the following areas where the malaria vector species are as specified:

Area	<i>Anopheles</i> species	Features
Tropical Africa, lowland, rural	<i>gambiae s.s.</i> , <i>funestus</i>	Highest human biting rates, therefore by far the highest malaria burden in the world
Tropical Africa, highland, rural	<i>gambiae s.s.</i> , <i>funestus</i>	Seasonal epidemics of malaria, therefore the human population develops little immunity
India, rural	<i>culicifacies</i> , sp.A	India uses more DDT than the whole of the rest of the world
South east Asia	<i>minimus</i> , <i>dirus</i>	Efficient vectors which do not rest indoors
Central America	<i>albimanus</i>	Bite out of doors early in the evening

In addition to the above suggestions for development of the project interventions under the program, STAP also notes some inconsistencies within the Annexes, referred to early in the proposal as: “The Strategic Programme will result in a yearly reduction of DDT application in vector management of about 4000 tons by the end of the Programme period (2014). Baseline estimates and indicators and targets for the Strategic Programme are attached as Annex 1.” However in Annex A on page 12, It seems incorrect to claim credit in this proposal for reduction in the use of 1,432 tons of DDT when this has already been achieved as a result of past activities (acknowledged in the text on the bottom of page 9). This amount is about 1/3 of the “proposed reductions” (4,000 tons/year), so it seems questionable to include this amount in the future overall benefits of implementing the program. STAP suggests reducing the total to 2,568 tons. Related to this, on page 13, referring to the questionable estimated DDT reintroductions (300 tons) in Papua New Guinea, Solomon Islands, Thailand,

Vanuatu, Vietnam, Philippines, Sri Lanka, Myanmar; is it therefore really reasonable to claim credit for a reduction of 300 tons in the overall total for the program?

Finally, there is no mention of China being included in this overall program. As China was a major producer, STAP wonders why this is the case.

<i>STAP advisory response</i>	<i>Brief explanation of advisory response and action proposed</i>
1. Consent	STAP acknowledges that on scientific/technical grounds the concept has merit. However, STAP may state its views on the concept emphasising any issues that could be improved and the proponent is invited to approach STAP for advice at any time during the development of the project brief prior to submission for CEO endorsement.
2. Minor revision required.	STAP has identified specific scientific/technical suggestions or opportunities that should be discussed with the proponent as early as possible during development of the project brief. One or more options that remain open to STAP include: (i) Opening a dialogue between STAP and the proponent to clarify issues (ii) Setting a review point during early stage project development and agreeing terms of reference for an independent expert to be appointed to conduct this review The proponent should provide a report of the action agreed and taken, at the time of submission of the full project brief for CEO endorsement.
3. Major revision required	STAP proposes significant improvements or has concerns on the grounds of specified major scientific/technical omissions in the concept. If STAP provides this advisory response, a full explanation would also be provided. Normally, a STAP approved review will be mandatory prior to submission of the project brief for CEO endorsement. The proponent should provide a report of the action agreed and taken, at the time of submission of the full project brief for CEO endorsement.