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ESSAY

Should the use of DDT be revived for malaria vector control?

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Indoor residual spraying with DDT was the principle method by which malaria transmission was eradicated or greatly reduced in many countries between the late 1940s and 1970s. Since then, decreasing use of DDT has been associated with a resurgence of malaria in India, Sri Lanka, former Soviet Central Asia, Zanzibar, Venezuela and several other Latin American countries. In India and Zanzibar, DDT resistance in vectors, as well as a decline in spray coverage, are probable causes of reduced effectiveness of DDT in recent decades. In southern Europe, eradication of malaria transmission was achieved by DDT spraying in the 1940s and 50s and eradication has been sustained by adequate treatment of imported human malaria cases. In the highlands of Madagascar and South Africa, recent reversion to DDT spraying has been successful in stemming resurgences of malaria. Continued use of DDT for vector control, but not for agriculture, is approved by the Stockholm Convention on Persistent Organic Pollutants. DDE residues in breast milk have been associated with DDT anti-malaria spraying in South Africa, but it is not known whether this is harmful. A claimed association of DDE residues with breast cancer have not been substantiated. There is a recent report of association of DDE residues with probability of premature birth; the possible relevance of this to anti-malarial use of DDT should be investigated. In Colombia, testing of the DDT stockpile for suspensibility, DDT resistance in *Anopheles darlingi* and investigation of the present affordability of widespread spraying with DDT, compared with alternative chemicals, are recommended.

Key words: indoor residual spraying, malaria eradication, malaria resurgence, DDT resistance, DDE in breast milk, DDE and breast cancer, DDE and premature birth, suspensibility of stockpiled DDT.

¿Debe regresar el uso del DDT para el control de vectores de la malaria?

La aspersión de DDT en las viviendas fue el principal método de erradicación de la transmisión de la malaria, o de una importante reducción, en muchos países durante las décadas del 40 al 70. Desde entonces, el uso cada vez menor del DDT se ha asociado con la reemergencia de la malaria en India, Sri Lanka, la región de Asia central de la antigua Unión Soviética, Zanzibar, Venezuela y varios países latinoamericanos. En India y Zanzíbar, la resistencia de los vectores al DDT, así como un descenso en las aspersiones, son las causas probables de la efectividad reducida del DDT en las últimas décadas. En el sur de Europa, la erradicación de la transmisión de la malaria se logró con el uso del DDT durante la década del 40 y el 50 y se ha mantenido con el manejo adecuado de los casos importados de malaria. En las tierras altas de Madagascar y Suráfrica, la reciente reutilización del DDT ha tenido éxito en detener el resurgimiento de la malaria. El uso continuo del DDT en el control de vectores, no en la agricultura, está aprobado por la Convención de Estocolmo sobre Contaminantes Orgánicos Persistentes. Los residuos de DDE en la leche materna se han asociado con la aspersión de DDT para el control de la malaria en Suráfrica, pero no se conoce si es dañino. No se ha probado la asociación de residuos de DDE con cáncer de seno. Existe un informe reciente de asociación de residuos del DDE con la probabilidad de nacimientos prematuros; se debe investigar la posible relevancia de esta asociación con el uso del DDT como antimalárico. En Colombia se ha recomendado la verificación del grado de suspensión del DDT almacenado, así como la resistencia de *Anopheles darlingi* al DDT y el estudio de la actual viabilidad del uso generalizado del DDT en comparación con otras sustancias alternativas.

Palabras clave: aspersión residual en interiores, erradicación de malaria, resurgimiento de malaria, resistencia a DDT, DDE en leche materna, DDE y cáncer de seno, DDE y nacimientos prematuros, suspensión de DDT almacenado.

Indoor residual spraying of DDT and what it can achieve

DDT for malaria vector control is not sprayed in the outdoor environment, as was the case with agricultural use of DDT in the past, but is used for indoor residual spraying of an aqueous suspension. The intention is that the DDT residue will adhere to the mosquito's legs when it rests on a sprayed wall or ceiling before or after blood feeding. Ideally, the amount of insecticide adhering is sufficient to kill the mosquito and permanently remove it from the potential vector population. Lesser amounts of insecticide irritate mosquitoes and drive them out of doors where they may bite animals and not humans.

Indoor residual spraying of DDT has been remarkably successful over many years since its inception in many parts of the world for control of malaria vectors and, in India, for the sandfly vectors of visceral leishmaniasis. When DDT indoor spraying has been withdrawn, frequently a resurgence of malaria has occurred, apparently because the extra cost of alternative insecticides has deterred malaria control organizations from continued treatment of all of the malarious parts of their countries. A survey of the malaria situation, before DDT treatment, at the peak of DDT spraying and after the peak, will be presented, starting with India and proceeding westward to Latin America.

Asia

After the discovery of the involvement of *Anopheles* mosquitoes in malaria transmission by Ross in India in 1897, unsuccessful attempts were made to control malaria in military camps by larval control. Until the 1940s, India had a massive malaria problem; about 75 million malaria cases with 0.75 million malaria deaths, and much visceral leishmaniasis. Since then it has been the largest user of DDT for vector control (1). In the 1960s use of this insecticide reduced malaria incidence nationwide to about 100,000 cases (i.e. about a 99.8% reduction), and visceral leishmaniasis was virtually eliminated. Malaria eradication was nearly, but not quite, achieved in the 1960s, when about 18,000 tons of DDT were sprayed annually. Subsequently, the momentum and funding for the eradication programme declined, because it was felt unjustified to spend a large proportion of the country's health budget on a disease which was nearly eradicated. In the 1990s only 7,500 tons of DDT were sprayed annually against malaria and visceral leishmaniasis. In parallel with this decline in spraying there has been resurgence of malaria in some parts of the country, but not to the very severe levels that had prevailed until the 1940s (2). Today, resistance has appeared to DDT (and to malathion also in some areas) in a few vector populations and, presumably at least partly for this reason, DDT is no longer as effective as it was. However, there is evidence that even where a standard WHO test only shows 11.5% mortality on DDT, spraying still has some effect (3), presumably because mosquitoes are diverted out of houses where they tend to bite cattle. India has always used a lower dose of DDT (1 g/m^2) than other countries, but there were no signs of improvement when the WHO standard of 2 g/m^2 was tested in India (3).

As mentioned, visceral leishmaniasis was virtually eliminated from north India as a side effect of DDT spraying directed against malaria vectors (4,5). The vector *Phlebotomus argentipes* was very endophilic and, therefore, vulnerable to indoor spraying. When DDT was not so actively sprayed, the vector and the disease have returned. According to WHO data, visceral leishmaniasis causes more loss of disability adjusted life years (DALY) in India than does malaria. Part of India's current consumption of DDT (which is manufactured in India and not exported) is specifically allotted to leishmaniasis control.

Continued use of DDT in India is doubtful since a total ban has influential support. Bio-environmental

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control of malaria vectors, using source reduction and larvivorous fish has been quite extensively tested in India (6). Studies have reported significantly lower levels DDT and/or DDE residues in soil, water and human blood in an area where bio-environmental control (and no insecticide) had been used for several years compared to an area with routine spraying (7). Very likely, these residues arose from illegal diversion of DDT intended for indoor spraying to agriculture. Advocates of bio-environmental control in India contend that these methods could cheaply and effectively replace almost all spraying except in epidemic conditions (6). Before accepting this argument, however, more comparative testing with indoor spraying must be undertaken in India's many different ecological situations, throughout the epidemic cycles which occur there and in routine use (not just as part of a trial by enthusiasts) against India's various vectors.

The history of malaria in Sri Lanka (8) is similar to that in India and the main vector, a member of the *Anopheles culicifacies* complex, is a close relative of the most important rural vector in India. After a history of severe epidemics in the 1930s (2-3 million cases and 80,000 deaths in 1934-35), DDT in Sri Lanka had dramatic effects in reducing malaria mortality in the 1950s. It was even more nearly successful than in India in achieving eradication -only 17 recorded cases in 1963. However, as in India, the priority given to malaria was downgraded when the battle was nearly won and resurgence as well as vector resistance occurred. Since the 1970s, the DDT resistance level was judged to be sufficiently high as to require a complete substitution by other insecticides, especially organophosphates and pyrethroids. Because of the greater cost of these insecticides, and the long continued civil war in the north of the island, spray coverage has not been as complete as in the 1950s and 60s. The incidence of the disease is, therefore, now much worse (about 360,000 cases in 1994) than in the 1960s, but not as bad as in the epidemics of the 1930s.

Despite its very cold winters, malaria was a serious problem in the USSR as far north as Moscow and across southern Siberia; in 1940 about 300,000 cases were reported. High malaria rates continued despite major efforts at mosquito larval control, using larvivorous fish, etc., and follow up of people infected with *Plasmodium vivax* in the winter and radical treatment of their infections (9). However, when DDT indoor residual spraying was added to this system of control, malaria was virtually eradicated in the 1950s and 60s though the disease was frequently re-introduced from Afghanistan. Later, malathion was used for spraying because of detection of DDT resistance in some of the vector populations. Now, with the decline of mosquito control and the health services generally, major malaria epidemics have appeared in the former Soviet Central Asian and Caucasian republics of Tadjikistan and Azerbaijan (about 15,000 cases in 1996 epidemics), as well as renewed transmission in the Ural Mountain region of Russia (10).

Africa

In the island of Zanzibar the highly efficient malaria vector *Anopheles gambiae* is present and, before the WHO supported anti-malaria campaign there, the disease was holoendemic in rural areas. The WHO campaign used DDT indoor residual spraying plus treatment of infected people with chloroquine; at that time no resistance to chloroquine had occurred. The campaign was remarkably successful (11) and lowered the infection in children to approximately 5%. This is much better than has been achieved in recent projects in Africa with insecticide treated nets. Unfortunately in 1968, the WHO team was expelled and malaria underwent a rapid resurgence. DDT resistance emerged after the spraying campaign had stopped. This was presumably a consequence of selection for resistance heterozygotes by decayed DDT residues which could not occur so long as the house surfaces were regularly re-sprayed. An attempt to revive DDT spraying was initiated in the 1980s with no success, presumably because of the resistance as well as inadequate coverage of houses. Malaria prevalence in rural areas has returned to holoendemic levels.

In the highlands of Madagascar, the climate is much cooler than in Zanzibar. Malaria was epidemic since introduction of rice growing in the 19th century. *Anopheles funestus* is the vector

and is very endophilic. At the end of the French colonial period in the 1950s an anti-malaria campaign was initiated based on DDT spraying and on compulsory treatment of schoolchildren with chloroquine. *A. funestus* and malaria reportedly disappeared completely from the highland area (12). Between the 1960s and 1980s, no anti-malaria activities were undertaken. Entomologists had observed *A. funestus* re-invading the highlands, and in the late 1980s a disastrous epidemic exploded in a population which by then was non-immune. An estimated 40,000 people died in the epidemic. With Italian aid, DDT spraying was re-introduced for a 5 year period in the 1990s; this brought *A. funestus* and malaria back under control (13). The intention now is to maintain surveillance and to re-spray any foci of disease which may emerge.

In South Africa, malaria was a major cause of mortality, morbidity and economic loss. Approximately 22,000 malaria deaths were recorded in 1931-32, with malaria morbidity paralysing the sugar industry (14). Indoor residual spraying with natural pyrethrum was attempted in the 1930s and DDT manufacture began in South Africa during the Second World War. Spraying of DDT was highly successful from 1945 to 1995 - *A. funestus* disappeared and the other vector, *Anopheles arabiensis*, was controlled and showed no signs of DDT resistance over that 50-year period. In 1995, South Africa's active environmentalist movement persuaded the government to ban DDT and to switch to pyrethroid spraying which, in short term trials, had appeared at least as effective as DDT. However, over the next four years, malaria case incidence increased at least fourfold. Considerable numbers of malaria deaths occurred, partly due to a very high level of resistance to sulfadoxine-pyrimethanine, a drug which was then the first line anti-malaria drug. Careful entomological studies showed that *A. funestus* had re-appeared, presumably by immigration from Mozambique, and was captured exiting alive from pyrethroid sprayed houses (15). Tests showed that these mosquitoes were resistant to pyrethroids, but not to DDT. In 2000, consultations led to agreement to switch back to DDT, which currently is purchased from China. Renewal of the use of DDT has been associated with a 60% reduction in cases during 2001 and disappearance of the problem of escape of *A. funestus* from sprayed houses. At the same time, artesunate became the first line anti-malaria drug; this has been associated with a near elimination of malaria deaths. It is important to emphasize that South Africa had the financial resources to continue with pyrethroid spraying; however, pyrethroid resistance prompted the switch back to DDT. Although DDT resistance had not been encountered in malaria vectors, DDT resistance has developed in bedbugs (*Cimex* spp.); fenitrothion has to be sprayed occasionally to control the bedbugs (16). DDT is sprayed only in mud-walled houses -the white deposit of 2g/m^2 DDT is considered intolerable on plastered walls. It is not known whether this leads to better malaria control among inhabitants of mud houses than houses with plastered walls.

Studies by Bouwman *et al*. (17) in South African villages with DDT anti-malaria spraying showed a much higher level of DDT and DDE in breast milk than in villages without anti-malaria spraying. The intake of 0.100 mg/kg/day of DDT + DDE by babies consuming this milk exceeds by 5 times the FAO defined allowable daily intake (ADI). This is disquieting, but it is not clear if these levels actually do any harm. It should be emphasized that ADI levels are specified on the assumption that they would continue throughout life.

DDT has been successfully used in other southern African countries, such as Swaziland, Botswana and Zimbabwe. In Swaziland, a switch from DDT to pyrethroids was never made and malaria control has remained very successful. A switch from DDT to pyrethroids may be considered necessary in Zimbabwe because of fears that DDT residues from indoor residual spraying would enter Zimbabwe's important tobacco crop and make it carcinogenic!

DDT has continued to be used in Ethiopia. Introduction or re-introduction of it in some East African countries is under discussion.

Europe

Malaria was important in Italy from the time of the Roman Empire (9). During the Mussolini regime in

the 1930s, energetic efforts were made at malaria control by drainage of vector breeding sites and use of quinine for case treatment. This reduced the problem, but still left about 55,000 cases per year at the beginning of the Second World War. The first anti-vector use of DDT occurred in Naples when, on the arrival of the U.S. Army in 1943, a louse borne typhus epidemic was found to be in progress. Compulsory mass treatment rapidly stopped this epidemic. DDT spraying against malaria was taken up immediately after the end of the war (late 1940s). The original plan made by Soper for Sardinia envisaged eradication of the vector *Anopheles labranchiae*. However, after 3 years, eradication had not been achieved but the effects of DDT in reducing survival of vectors and/ or diverting them from biting humans had so reduced transmission that eradication was achieved, first of *Plasmodium falciparum* and then of *Plasmodium vivax*. Since the 1950s, DDT has not been sprayed and malaria transmission has not re-appeared (apart from one or two cases) although the potential vector populations are again present in a favourable climate for transmission. This is despite many imported cases among Italians who have travelled to the tropics. They have access to a good medical system and if they develop malaria symptoms they receive prompt treatment, generally before gametocytes develop in their bloodstream. Therefore, these cases are unlikely to infect local mosquitoes.

A similar history of successful and persistent eradication by use of DDT, backed up by effective drug treatment, has been seen in Greece, Cyprus, Spain, Portugal, Yugoslavia and its successor states.

Latin America

One of the first DDT campaigns against malaria was that initiated by Gabaldón in Venezuela (18). Like much of tropical Latin America, very high rates of malaria mortality were present in the 1930s. However, malaria was eliminated when a DDT spraying campaign was undertaken in most of the northern, developed, parts of the country. Only where very exophilic vectors, such as *Anopheles nuneztovari,* existed did malaria transmission continue. More recently, as the amount of DDT and other insecticide spraying has declined, malaria resurgence has occurred in several areas and about 24,000 cases were recorded in 1990s.

Data of Roberts *et al.* (19) show a similar resurgence in six other Latin American countries (including Colombia) where DDT consumption has declined or been eliminated. No doubt that some of the malaria resurgence is due to non-insecticidal factors such as colonization of the Brazilian Amazon. However, the fact that for a time in the 1990s Ecuador increased its DDT usage and saw a decline in malaria, surely indicates that more spraying has the potential to improve the situation.

The most important Latin American vector, *Anopheles darlingi,* is generally considered susceptible to DDT; this was confirmed in Meta and Bolívar, Colombia (20). However, resistance was detected a decade ago in Quibdó, Colombia, using the standard WHO test papers impregnated with 4% DDT solution (20). In contrast, bioassays on *A. darlingi* from this area on deposits at the standard spraying dose of 2 g/m^2 still gave high mortality. It would be of interest to investigate whether, in the absence of DDT spraying in recent years, the resistance gene has declined in frequency under natural selection and whether or not resistance would now prevent effective use of DDT in any parts of Colombia. More expensive insecticides might be required in certain areas but, bearing in mind the Indian data (3), DDT may be far from useless in the field even if WHO tests show poor mortality in the laboratory.

Colombia reportedly retains a considerable store of unused DDT. A WHO recommended methodology is available (see WHO Pesticide Evaluation Scheme website) to check stored DDT for adequate suspensibility so that when mixed with water it will remain in suspension for long enough for effective application.

Some comments on toxicity of DDT

Many otherwise well informed people believe that 'everyone knows' that DDT is a deadly, dangerous chemical. When used on a large scale, out of doors, in agriculture, in the 1950s, it sometimes harmed fish and it accumulated in food chains and reduced the hatchability of eggs of attractive birds such as falcons. For those reasons it was

banned in most developed countries in the 1970s (21).

If DDT is to be used for vector control, effective regulation must be instituted to prevent illegal diversion of DDT to agricultural use, both because of possible harm to wild life and because residues can appear in export products. Such residues may be detectable by very sensitive modern analytical methods and may make the product unacceptable by importers, even in the absence of evidence that the residues are harmful.

Many claims have been made about toxicity of DDT to humans but most have not withstood careful investigation. A thorough study of the health of men who had worked for years as DDT spray men showed no significant excess prevalence of any disease in them compared with matched controls (22).

The oestrogen mimetic properties of DDT were claimed to have been the cause of the decline in human sperm counts. However, disentangling the possible influence of DDT from that of many bio-active industrial products is difficult. India has had the largest consumption of DDT for malaria control and low human fertility does not seem to be a problem there.

Earlier claims of carcinogenicity of DDT were based on finding significantly more of the DDT derivative, DDE, in the serum of patients dying of cancer compared with healthy controls. However, emaciated cancer patients apparently liberate into their serum DDE which normally is harmlessly stored in their body fat. Thus, the cancer may be considered to have caused the elevated serum DDE, rather than the DDE causing the cancer. A better study design was adopted by Wolff *et al.* (23) who worked from frozen stored serum samples; they compared DDE content in women who were later found to have developed breast cancer, compared with matched controls. These data showed that the ratio of DDE content for patients compared with controls was about 1.4, with a lower 99% confidence limits just above 1.0. However, a meta-analysis of six similar studies did not confirm a significant association of DDE with likelihood of developing breast cancer (24).

A recent study was based on serum samples from the USA stored in the 1950s and 60s, when there was considerable contamination of food from agricultural use of DDT. It showed a significant association of DDE content with probability of a pre-term delivery and/or an underweight baby (25). The reasons for acquisition of very different levels of DDE by different individuals from their diets is not known, and the authors refer to a possible connection with albumen levels in the blood. Quite possibly the underlying causes of variation in DDE are confounding factors affecting probability of pre-term birth. Further studies are recommended that could more directly associate DDE acquired from DDT anti-malaria spraying, with pre-term births. One has to recognize that pre-term births are associated with infant mortality and one must consider the possibility that DDE might cause more infant mortality than effective malaria control prevents.

Until recently, advocating serious studies of claims about DDT toxicity was usually met with the response that DDT is already banned or about to be banned and, hence, further studies are not worthwhile. However, in the text of the Stockholm Convention on Persistent Organic Pollutants, which was finalized in Johannesburg in December 2000, an amendment was incorporated which authorizes continued use of DDT for vector control, but not for agriculture. This wording was approved without dissent by the approximately 150 national delegations present. The only provisos are that UNEP is informed and that WHO guidelines are followed, i.e., that the DDT is of adequate quality and that DDT resistance in the local vector is not at a level that would prevent an impact on malaria.

Conclusions

The following suggestions are offered which would help to decide Colombia's future policy with regard to reviving DDT for malaria vector control:

1) Support is recommended for studies that can confirm or deny the possibility that DDT, as formulated for use in malaria control, is associated with pre-term births, and that vigilance be maintained for other possible adverse effects.

2) Determine if resistance to DDT in *A. darlingi* in different parts of Colombia is at a level which will

seriously interfere with effective use of this insecticide against malaria.

3) Determine the suspensibility of the DDT in Colombia's current stockpile.

4) Compare the price per household protected per year of a new supply of DDT manufactured in China or elsewhere, with that of effective alternatives. Assess whether the higher cost of alternatives to DDT would reduce the proportion of Colombia's malarious areas with available resources.

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