Cochrane Library

Cochrane Database of Systematic Reviews

Indoor residual spraying for preventing malaria (Review)

Pluess B, Tanser FC, Lengeler C, Sharp BL

Pluess B, Tanser FC, Lengeler C, Sharp BL.
Indoor residual spraying for preventing malaria.
Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD006657.
DOI: 10.1002/14651858.CD006657.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 3
OBJECTIVES . . . 4
METHODS . . . 4
RESULTS . . . 7
Figure 1. . . . 9
Figure 2. . . . 10
DISCUSSION . . . 12
AUTHORS' CONCLUSIONS . . . 13
ACKNOWLEDGEMENTS . . . 14
REFERENCES . . . 14
CHARACTERISTICS OF STUDIES . . . 22
ADDITIONAL TABLES . . . 39
WHAT'S NEW . . . 45
HISTORY . . . 45
CONTRIBUTIONS OF AUTHORS . . . 45
DECLARATIONS OF INTEREST . . . 45
SOURCES OF SUPPORT . . . 46
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 46
INDEX TERMS . . . 46

[Intervention Review]

Indoor residual spraying for preventing malaria

Bianca Pluess[1], Frank C Tanser[2], Christian Lengeler[1], Brian L Sharp[3]

[1]Public Health and Epidemiology, Swiss Tropical and Public Health Institute, Basel, Switzerland. [2]Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Mtubatuba, South Africa. [3]Malaria Research Lead Programme, Medical Research Council, Durban, South Africa

Contact address: Christian Lengeler, Public Health and Epidemiology, Swiss Tropical and Public Health Institute, Basel, 4002, Switzerland. Christian.Lengeler@unibas.ch.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: Unchanged, published in Issue 5, 2019.

Citation: Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. *Cochrane Database of Systematic Reviews* 2010, Issue 4. Art. No.: CD006657. DOI: 10.1002/14651858.CD006657.pub2.

ABSTRACT

Background

Primary malaria prevention on a large scale depends on two vector control interventions: indoor residual spraying (IRS) and insecticide-treated mosquito nets (ITNs). Historically, IRS has reduced malaria transmission in many settings in the world, but the health effects of IRS have never been properly quantified. This is important, and will help compare IRS with other vector control interventions.

Objectives

To quantify the impact of IRS alone, and to compare the relative impacts of IRS and ITNs, on key malariological parameters.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (September 2009), CENTRAL (*The Cochrane Library* 2009, Issue 3), MEDLINE (1966 to September 2009), EMBASE (1974 to September 2009), LILACS (1982 to September 2009), *m*RCT (September 2009), reference lists, and conference abstracts. We also contacted researchers in the field, organizations, and manufacturers of insecticides (June 2007).

Selection criteria

Cluster randomized controlled trials (RCTs), controlled before-and-after studies (CBA) and interrupted time series (ITS) of IRS compared to no IRS or ITNs. Studies examining the impact of IRS on special groups not representative of the general population, or using insecticides and dosages not recommended by the World Health Organization (WHO) were excluded.

Data collection and analysis

Two authors independently reviewed trials for inclusion. Two authors extracted data, assessed risk of bias and analysed the data. Where possible, we adjusted confidence intervals (CIs) for clustering. Studies were grouped into those comparing IRS with no IRS, and IRS compared with ITNs, and then stratified by malaria endemicity.

Main results

IRS versus no IRS

Stable malaria (entomological inoculation rate (EIR) > 1): In one RCT in Tanzania IRS reduced re-infection with malaria parasites detected by active surveillance in children following treatment; protective efficacy (PE) 54%. In the same setting, malaria case incidence

assessed by passive surveillance was marginally reduced in children aged one to five years; PE 14%, but not in children older than five years (PE -2%). In the IRS group, malaria prevalence was slightly lower but this was not significant (PE 6%), but mean haemoglobin was higher (mean difference 0.85 g/dL).

In one CBA trial in Nigeria, IRS showed protection against malaria prevalence during the wet season (PE 26%; 95% CI 20 to 32%) but not in the dry season (PE 6%; 95% CI -4 to 15%). In one ITS in Mozambique, the prevalence was reduced substantially over a period of 7 years (from 60 to 65% prevalence to 4 to 8% prevalence; the weighted PE before-after was 74% (95% CI 72 to 76%).

Unstable malaria (EIR < 1): In two RCTs, IRS reduced the incidence rate of all malaria infections;PE 31% in India, and 88% (95% CI 69 to 96%) in Pakistan. By malaria species, IRS also reduced the incidence of *P. falciparum* (PE 93%, 95% CI 61 to 98% in Pakistan) and *P. vivax (*PE 79%, 95% CI 45 to 90% in Pakistan); There were similar impacts on malaria prevalence for any infection: PE 76% in Pakistan; PE 28% in India. When looking separately by parasite species, for *P. falciparum* there was a PE of 92% in Pakistan and 34% in India; for*P. vivax* there was a PE of 68% in Pakistan and no impact demonstrated in India (PE of -2%).

IRS versus Insecticide Treated Nets (ITNs)

Stable malaria (EIR > 1): Only one RCT was done in an area of stable transmission (in Tanzania). When comparing parasitological re-infection by active surveillance after treatment in short-term cohorts, ITNs appeared better, but it was likely not to be significant as the unadjusted CIs approached 1 (risk ratio IRS:ITN = 1.22). When the incidence of malaria episodes was measured by passive case detection, no difference was found in children aged one to five years (risk ratio = 0.88, direction in favour of IRS). No difference was found for malaria prevalence or haemoglobin.

Unstable malaria (EIR < 1): Two studies; for incidence and prevalence, the malaria rates were higher in the IRS group compared to the ITN group in one study. Malaria incidence was higher in the IRS arm in India (risk ratio IRS:ITN = 1.48) and in South Africa (risk ratio 1.34 but the cluster unadjusted CIs included 1). For malaria prevalence, ITNs appeared to give better protection against any infection compared to IRS in India (risk ratio IRS:ITN = 1.70) and also for both *P. falciparum* (risk ratio IRS:ITN = 1.78) and *P. vivax* (risk ratio IRS:ITN = 1.37).

Authors' conclusions

Historical and programme documentation has clearly established the impact of IRS. However, the number of high-quality trials are too few to quantify the size of effect in different transmission settings. The evidence from randomized comparisons of IRS versus no IRS confirms that IRS reduces malaria incidence in unstable malaria settings, but randomized trial data from stable malaria settings is very limited. Some limited data suggest that ITN give better protection than IRS in unstable areas, but more trials are needed to compare the effects of ITNs with IRS, as well as to quantify their combined effects. Ideally future trials should try and evaluate the effect of IRS in areas with no previous history of malaria control activities.

PLAIN LANGUAGE SUMMARY

Indoor residual spraying for preventing malaria

Spraying houses with insecticides (indoor residual spraying; IRS) to kill mosquitoes is one of the main methods that have been used to control malaria on a large scale. IRS has helped to eliminate malaria from great parts of Asia, Russia, Europe, and Latin America, and successful IRS programmes have also been run in parts of Africa.

Another successful method of mosquito control relies on the use of physical barriers such as bednets or curtains that can also be sprayed with insecticides (insecticide treated nets; ITN). This review aims to look at the health benefits of IRS and to compare this method with ITNs.

This review does not assess the potentially adverse effects of insecticides used for IRS, and it includes not only randomized controlled trials (RCTs), but also controlled before-and-after studies (CBA) and interrupted time series (ITS), as these methods were considered suitably rigorous.

Six studies were identified for inclusion (four cluster RCTs, one CBA and one ITS). Four of these studies were conducted in sub-Saharan Africa, one in India and one in Pakistan. IRS reduced malaria transmission in young children by half compared to no IRS in Tanzania (an area where people are regularly exposed to malaria), and protected all age groups in India and Pakistan (where malaria transmission is more unstable and where more than one type of malaria is found).

When compared with ITNs, IRS appeared more protective (according to the outcome chosen) in one trial conducted in an area of stable malaria transmission, but ITN seemed to be more protective than IRS in unstable areas. Unfortunately, the level of evidence is very limited and no firm conclusions should be drawn on the basis of this review.

In conclusion, although IRS programmes have shown impressive success in malaria reduction throughout the world, there are too few well-run trials to be able to quantify the effects of IRS in areas with different malaria transmission, or to properly compare IRS and ITN. High-quality and long-duration trials on a large scale, done in areas where there has been little or no mosquito control are still urgently required. New trials should include an IRS arm and an ITN arm, and should also assess the combined effect of ITN and IRS, a very important question in view of malaria elimination.

BACKGROUND

There were an estimated 247 million malaria cases among 3.3 billion people at risk in 2006, causing nearly one million deaths, mostly of children under five years. One hundred and nine countries were endemic for malaria in 2008, 45 within the WHO African region (WHO 2008). Ninety per cent of all malaria cases occur in sub-Saharan Africa, in areas of stable endemic transmission, and around 20% of all deaths in children have been attributed directly to malaria (Snow 1999). The disease causes widespread premature death and suffering, imposes financial hardship on poor households, and holds back economic growth and improvements in living standards. The rapid spread of resistance first to chloroquine and now to sulfadoxine-pyrimethamine has greatly increased the cost and difficulty of malaria case management, particularly in Africa (RBM 2005). Estimates have suggested that malaria costs the African countries US$12 billion annually and may considerably retard economic development (Sachs 2002).

Primary prevention of malaria is essentially achieved through two main vector control interventions: indoor (house) residual insecticide spraying (IRS); and insecticide-treated (mosquito) nets (ITNs). The health effects of ITNs have been comprehensively summarized in two Cochrane Reviews, one for general populations (Lengeler 2004) and one for pregnant women (Gamble 2006).

IRS has a long and distinguished history in malaria control. Using mainly dichloro-diphenyl-trichlorethane (DDT), malaria was eliminated or greatly reduced as a public health problem in Asia, Russia, Europe, and Latin America (Schiff 2002; Lengeler 2003; Roberts 2004). IRS continues to be used in many parts of the world, with the services provided by the public health system or by a commercial company (usually for the benefit of its employees). There is no IRS programme known to us in which beneficiaries were expected to contribute financially.

A historical review of IRS in Southern Africa investigated the malaria situation before and after the introduction of IRS in South Africa, Swaziland, Namibia, Zimbabwe, and Mozambique, where it continues to protect 13 million people (Mabaso 2004). After the implementation of control operations, spectacular reductions in malaria parameters and vector densities were recorded, and in certain instances the intervention led to local elimination. Another historical paper reviewed the health impacts of 36 successful IRS programmes in 19 countries throughout sub-Saharan Africa (Kouznetsov 1977). The analyses compared parasite rates and other malariological outcomes before and after the operation in each of the five major eco-epidemiological zones and demonstrated substantial epidemiological benefits. Unfortunately, most of these studies simply documented time trends of malaria parameters with no appropriate control groups. This is also the case for the most recent programme impact assessments (Sharp 2002; Tseng 2008;Teklehaimanot 2009; Kleinschmidt 2009). Hence, while there is no doubt that IRS reduces malaria transmission and improves health outcomes, assessments up to the present day do not allow us to quantify the health effects.

IRS is thought to operate both through repelling mosquitoes from entering houses and by killing female mosquitoes that are resting inside houses after having taken a blood meal. This implies that IRS is most effective against mosquito species that are resting indoors (so called endophilic mosquitoes). Whereas ITNs show a high degree of personal protection, IRS relies largely on a vectorial *mass effect*: the increased mortality of adult vectors mostly following feeding leads to a reduction in transmission. Spraying needs to be carried out between once and three times per year; the timing depending on the insecticide and the seasonality of transmission in a given setting. Reviewing the advantages and disadvantages of each insecticide is beyond the scope of this review and can be found among other in Najera 2001.

IRS has the advantage of being able to make use of a much wider range of insecticide products in comparison to ITNs, for which pyrethroids are the only class of insecticide currently used. The World Health Organization (WHO) recommends a number of insecticides for individual residual spraying: DDT wettable powder (WP); malathion WP; fenitrothion WP; pirimiphos-methyl

WP and emulsifiable concentrate (EC); bendiocarb WP; propoxur WP; alpha-cypermethrin WP & suspension concentrate (SC); cyfluthrin WP; deltamethrin WP; etofenprox WP; lambda-cyhalothrin capsule suspension (CS) and WP (WHOPES 2007). This extended range of insecticides has important benefits for the management of insecticide resistance and hence the long-term sustainability of vector control (pyrethroid resistance has already been reported in many parts of tropical Africa and other parts of the world among populations of the major malaria vectors). The potentially adverse effects of insecticides used for IRS, especially DDT, is an important issue but one that is beyond the scope of this review.

Insecticide spraying is often done on a very large scale in order to maximize the mass effect of the insecticide; thus randomized controlled trial (RCT) designs may not always be feasible. However, controlled before-and-after studies (CBA) are clearly feasible, as are interrupted time series (ITS). We plan to include these three study designs while excluding simple pre-test and post-test studies with no concurrent controls, as the many potential biases make interpretation a problem. In all identified studies, allocation is expected to be by clusters rather than by individuals, since IRS is thought to be only effective if a large proportion of the population is protected.

Two reviews have outlined the cost and health effects of IRS (Curtis 2001; Lengeler 2003) including a comparison of IRS against ITNs, but neither was conducted systematically or assessed the methodological quality of the included studies. Yukich 2008 presented standardized cost and cost-effectiveness assessments for the major ITN distribution models as well as for two IRS programmes in Southern Africa.

Here we aim to quantify the health benefits of IRS and to compare how IRS and ITNs differ in their ability to prevent ill-health from malaria.

OBJECTIVES

To quantify the impact of IRS alone, and to compare the relative impacts of IRS and ITNs, on key malariological parameters.

METHODS

Criteria for considering studies for this review

Types of studies

1. **RCTs and quasi-RCTs**, randomized by cluster (cluster RCTs) and with three or more units per arm Bennett 2002; because of the mode of action of IRS (relying on a *mass effect*) we did not expect to find trials with individual randomization.
2. **Controlled before-and-after studies** with (1) two or more units per arm, (2) a contemporaneous control group, (3) monitoring of at least one transmission season before and after the intervention and (4) at least 60% coverage in the intervention arm.
3. **Interrupted time series**, with (1) a clearly defined point in time when the intervention occurred, (2) monitoring of at least two transmission seasons before and after the intervention and (3) at least 60% coverage in the intervention arm.

Types of participants

Children and adults living in rural and urban malarious areas.
Excluded: studies examining the impact of IRS on soldiers, refugees, industrial workers and other special groups not representative of the general population.

Types of interventions

Interventions

IRS carried out with insecticides recommended by the WHO at the correct dosage (WHO 2006; WHOPES 2007). Selected insecticides should not have been used where site-specific insecticide resistance has been reported by the authors or in other available literature. To this effect, we searched for publications on insecticide resistance for each included trial site. Coverage of houses should have been above 60%.
For the comparison with ITNs, we used the same inclusion criteria as in Lengeler 2004: mosquito nets treated with a synthetic pyrethroid insecticide at a minimum target dose of: 200 mg/m^2 for permethrin and etofenprox; 30 mg/m^2 for cyfluthrin; 20 mg/m^2 for alphacypermethrin; and 10 mg/m^2 for deltamethrin and lambdacyhalothrin.

Controls

- Should not have received another insecticide-based malaria intervention.
- Should not have received a malaria-co-intervention(s) that differed from the intervention arm.
- ITNs only for the comparison IRS versus ITNs. For this comparison we made a distinction between situations in which ITNs were distributed to a population previously protected by IRS (which was obviously stopped for the time of the study) and situations in which the distribution of ITNs represents the first vector control intervention. Obviously, in a population previously protected by IRS the vector population would have been affected and it was assumed that this would have an effect on how well ITNs would work subsequently.

Types of outcome measures

Before the start of the review the following standardized outcomes were specified:

- All cause child mortality: children aged < 10 years, mortality determined by a prospective demographic surveillance system.
- Severe disease: site-specific definitions based on the WHO guidelines WHO 2000. The definition includes demonstration of parasitaemia. Cerebral malaria is defined as coma or prostration and/or multiple seizures. The cut-off for severe, life-threatening anaemia is set at 5.1 g/L.
- Uncomplicated clinical malaria episodes: site-specific definitions, including fever, usually with parasitological confirmation, detected passively or actively. The case definition must be similar in all trial arms for the trial to be included in the analysis.
- Incidence of re-infections (after treatment): incidence rate of parasitaemia following radical cure; done with cohorts of children over 8 weeks.
- Parasite prevalence: obtained using a site-specific method for estimating parasitaemia, usually thick and/or thin blood smears.
- High density malaria prevalence: same as for parasite prevalence but with a site-specific parasitological cut-off.
- Haemoglobin levels (g/dL).
- Standard anthropometric measures: weight-for-age, height-for-age, weight-for-height, skinfold thickness, and/or mid-upper arm circumference.
- Splenomegaly: measured using Hackett's scale from 1 to 5.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). For details see Table 1.

Databases

On 16 September 2009 we searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) as published in *The Cochrane Library*; MEDLINE; EMBASE; and LILACS. We also searched the *meta*Register of Controlled Trials (*m*RCT) using 'insecticide$' and 'malaria' as search terms.

Agencies and manufacturers

We contacted the following agencies, which have funded malaria control studies, for unpublished and ongoing trials: World Bank; UNICEF; World Health Organization; PAHO; and USAID. We also contacted the following manufacturers of insecticides: Bayer; BASF; Sumitomo; and Syngenta (June-July 2007). In June 2007 we also searched the US Armed Forces Pest Management Board web site for relevant trials, as well as all other sources that we identified in the process of the search.

Reference lists

We checked the reference lists of all studies identified by the above methods.

Data collection and analysis

1. Study selection

BP screened the results of the search strategy for potentially relevant studies and retrieved full articles. BP and FT independently assessed all identified studies for inclusion in the review, using an eligibility form based on the inclusion criteria. We scrutinized each report to avoid study duplication. We attempted to contact the study authors for clarification if it was unclear whether a study met the inclusion criteria or if there were issues with the study design. CL was asked to resolve any differences in opinion. We explain below the reasons for excluding studies ("Characteristics of excluded studies").

2. Assessment of methodological quality

BP/FT and CL independently evaluated the methodological quality of each included study. We attempted to contact the study authors if key information was missing or unclear, and resolved any disagreements through discussion.

2.1. RCTs

BP assessed the risk of bias of each included trial using The Cochrane Collaboration's risk of bias tool (Higgins 2008). We followed the guidance tool to make judgements on the risk of bias in six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias. We categorized these judgements as 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear'.

2.2. Controlled before-and-after studies

We followed a strategy published elsewhere (Adinarayanan 2007); BP and FT independently assessed the quality of the included CBA study using a variety of criteria that we considered important and had specified *a priori*. These included: high intervention coverage in the community of interest (defined as at least 60% IRS

coverage), presence of some type of comparison group with no intervention, reporting of outcomes for the entire community. We also attempted to identify concurrent control activities carried out at the same time or just before the IRS intervention by screening the primary study report and other relevant literature.

2.3. Interrupted time series

We used the criteria published elsewhere (EPOC 2002) to assess the study quality of the one included study. Criteria included protection against secular changes, sufficient data points to enable reliable statistical inference, protection against detection bias, and completeness of the data set. We also attempted to identify concurrent control activities carried out at the same time or just before the IRS intervention by screening the primary study report and other relevant literature.

3. Data extraction

BP independently extracted the data from each study into standardized data extraction forms. Again, we attempted to contact the corresponding author in any case of unclear or missing data.

3.1. RCTs

We extracted data according to the intention-to-treat principle: if any individual allocated to a treatment group was analysed as if the person had effectively received the intervention. If there was discrepancy between the number of units/participants randomized and the number of units/participants analysed we calculated the percentage losses to follow-up in each group and reported this information. In trials that compared ITNs with IRS, we assessed the differences in coverage between the different groups and presented this information in a table.

Cluster RCTs: Where results have been adjusted for clustering, we extracted the point estimate and the 95% confidence interval (CI). If the results were not adjusted for clustering, where possible we extracted outcome data as for individual RCTs and corrected the data in the analysis. We always recorded the number of clusters, the average size of clusters, and the unit of randomizations (eg household, village or other). The statistical methods used to analyse the trials are described below in section 4.1.

3.2. Controlled before-and-after studies

We extracted data using the same methods as for the RCTs, but we added information on the comparability of baseline characteristics and the time period of data collection.

3.3. Interrupted time series

We extracted data using the same methods as for the RCTs, but we added information on the comparability of baseline characteristics and additional information relating to the assessments made before and after the initiation of the intervention, using the approach recommended by EPOC 2002.

4. Data analysis

4.1. Cluster RCT

We had planned to meta-analyse the data from RCTs using Review Manager 5. However, the number of the trials was too low to meaningfully do such a meta-analysis. Hence we have only presented a narrative or tabulated summary of all study data.

All results are either presented as rates/proportions or as Risk Ratios (RR). From the RR the protective efficacy (PE; expressing the percentage reduction in an outcome) was derived using the formula: PE = (1- RR) * 100.

Cluster RCTs with two or three arms and at least three clusters per arm were used for the comparisons of IRS versus no intervention or IRS versus ITNs. Three clusters per arm is considered a minimum (1) to minimize the risk of imbalances between groups, and (2) to allow appropriate statistical analysis (Bennett 2002). The two other study designs (CBA and ITS) were used only for the comparison of IRS versus no intervention.

Cluster trials require a more a complex analysis than that for individual RCTs (Hayes 2000). Observations on participants in the same cluster tend to be correlated and that intra-cluster variation must be accounted for during the analysis. If this correlation is ignored in the analysis the measure of effect remains a valid estimate but the associated variance of the estimate would be underestimated, leading to unduly narrow CIs.

For dichotomous outcomes expressed as risk, the results can be adjusted for clustering by multiplying the standard errors of the estimates by the square root of the design effect, where the design effect is calculated as DEff=1+(m-1)*ICC. This requires information such as the average cluster size (m) and the intra-cluster correlation coefficient (ICC). Unfortunately, the ICC was never reported by trial authors and hence cluster-adjustment was not always possible post-hoc. When the unadjusted CIs did not demonstrate a significant difference, then this is indicated.

For dichotomous outcomes expressed as rates, we applied the methods described in (Bennett 2002) using a rate ratio calculated from the mean incidence rates for each treatment group. In the case of the study by Misra 1999 the authors used a geometric mean of the incidence rates and we applied the method described by Bennett 2002 using a rate ratio based on the geometric mean incidence rates for the outcomes "*P. vivax* and *P. falciparum* combined".

Heterogeneity: With enough trials we would have assessed heterogeneity by (1) inspecting the forest plots to detect overlapping CIs, (2) applying the Chi^2 test with a P value of 0.10 indicating statistical significance, and (3) implementing the I^2 statistic with a value of 50% denoting moderate levels of heterogeneity. However, the number of trials was so low that combining trials was not possible. We stratified the presentation of the results into two groups on the basis of the entomological inoculation rate (EIR; number of infected bites per person per day) where < 1 was considered unstable malaria transmission, while settings with an EIR > 1 were considered to have stable transmission. A stratification on the basis of the main types of vectors, types of insecticides and other important factors was not possible because of the low number of trials. Where possible the analysis was stratified by parasite species (*P. falciparum* and *P. vivax)*. Finally, consideration was given to the fact that in some areas the vector control activities have gone on for many years before the reported study, while in some other situations the investigated study introduced the vector control activities. While we have at present no way to assess the effect of this difference, areas having had vector control for a long time are clearly different from areas with no previous activities in many different aspects (entomological and human health parameters).
Sensitivity analysis: There weren't sufficient trials to conduct a sensitivity analysis to investigate the robustness of the results.

4.2. Controlled before-and-after studies

We analysed the study in the same manner as RCTs and presented the results in tables.

4.3. Interrupted time series

We analysed the study in the same manner as RCTs and presented the results in tables.

RESULTS

Description of studies

Results of the search

We identified 134 potentially relevant studies. Of these we excluded 128 studies (for details of reasons see below and "Characteristics of excluded studies"). The remaining six studies met all the inclusion criteria. These trials are described below (for details see also "Characteristics of included studies").

Included studies

Trial design and location

Out of the six included studies, four were RCTs (Curtis 1998; Misra 1999; Mnzava 2001; Rowland 2000), and in all of these the allocation was by cluster (by villages, geographical blocks and sectors comprising several villages). One study was a CBA (Molineaux 1980) and one was an ITS (Sharp 2007).
Four trials were conducted in sub-Saharan Africa: Tanzania (Curtis 1998), South Africa (Mnzava 2001), Nigeria (Molineaux 1980) and Mozambique (Sharp 2007);one was conducted in Pakistan (Rowland 2000) and one in India (Misra 1999).
Three trials were in areas with stable transmission (EIR>1) and three in areas with unstable transmission (EIR<1) (Table 2).

Participants

The trials included either all ages (Misra 1999; Mnzava 2001; Molineaux 1980; Sharp 2007 for first year) or specific age groups (different groupings among children aged one to 15 years)(Curtis 1998; Rowland 2000; Sharp 2007 for subsequent years).

Intervention

RCT:

One trial compared the impact of IRS versus the provision of ITNs to all inhabitants (Mnzava 2001). Two trials had three arms and compared the impact of IRS to the impact of ITN and to an untreated control zone (Curtis 1998; Misra 1999). One trial studied the impact of IRS in comparison to a control area without any intervention (Rowland 2000). For IRS, all studies used pyrethroids as insecticide. Two of them used deltamethrin (dosage = 20 mg/m²), and the two others lambdacyhalothrin (30 mg/m²) and alphacypermethrin (25 mg/m²). Since there is no evidence to suggest that there is a difference between these insecticides in terms of impact they were grouped for analysis. Two trials did not specifically report the spray coverage (Mnzava 2001; Curtis 1998) but oral communication from the investigators suggested coverage was "high"; for the other two (Misra 1999; Rowland 2000) coverage ranged from 92.2% to 96%. For treating ITNs, lambdacyhalothrin (10 mg/m² and 20 mg/m²), deltamethrin (25 mg/m²) and permethrin (200 mg/m²) were used. Again, available evidence (Lengeler 2004) does not suggest any difference in impact between these three pyrethroids. Coverage rates with ITNs ranged in two trials from 85.4% to 100% (Misra 1999; Mnzava 2001), while one trial didn not report coverage (Curtis 1998) but it was "high" since nets were given for free to the whole population (Curtis C. personal communication).

In two of the three trials comparing IRS with ITNs (Mnzava 2001) IRS was done in the ITN areas before these were distributed. In the study area in KwaZulu-Natal there is a long history of IRS (around 50 years). Within the study area, all the houses in the ITN arm were sprayed in September 1996 before distributing the ITNs in January 1997. In subsequent years, house spraying was deliberately withdrawn in blocks with bed nets. In India (Misra 1999) there was a similar situation because of the long history of IRS in the study area, which started in 1953. IRS is nowadays a mainstay of malaria control in the study area.

CBA:

The impact of IRS was compared to a control area without any intervention (Molineaux 1980). Propoxur (2 g/m²) was used as insecticide. The spray coverage ranged from 74% to 100%. There was no history of IRS in the area before this trial.

ITS:

In the study of Sharp 2007 the change over time due to IRS was examined over the time period of two years before and five years after the introduction of IRS. The insecticide used was bendiocarb (400 mg/m²) and no usage coverage was mentioned. No history of IRS has been reported within the area before this study.
Some additional characteristics of the trials are given in Table 2.

Outcomes

Prevalence and incidence of malaria infections were the main outcomes that we could assess. See Table 3 for details.
Five studies looked at the prevalence rates of parasitaemia. Of these, two RCTs (Misra 1999; Rowland 2000) were conducted in unstable malaria settings and one RCT (Curtis 1998), one ITS (Sharp 2007) and one CBA (Molineaux 1980) in stable malaria settings.
The incidence rate of malaria infections (local case definitions) was assessed in four studies. Of these, three RCTs were conducted in unstable malaria settings (Rowland 2000; Misra 1999; Mnzava 2001) and one RCT (Curtis 1998) in a stable malaria setting.
In one setting (Curtis 1998) the authors also reported incidence of re-infections in multiple short-term cohorts of children (seven to eight weeks) following radical cure.
Impact on infant parasitological conversion rates was measured by Molineaux 1980, while anaemia as additional outcomes was collected in a stable malaria settings by Curtis 1998.
Infant mortality rates were measured by Molineaux 1980 but unfortunately not in a suitable control area, and hence this outcome could not be used.

Excluded studies

One hundred and twenty-eight studies were excluded due to the following reasons (for details see table "Characteristics of excluded studies"):

- 40 did not have enough units/arm (minimum required: RCT: 3 clusters per arm, CBA: 2 clusters per arm)
- 22 did not have control sites which were comparable with the intervention sites
- 8 used an insecticide or a dosage not recommended by WHO
- 12 were only reviews or conference abstracts and did not provide enough data
- 28 were ITS which did not provide enough data for pre- or post-intervention assessment
- 14 were ITS using a mix of interventions
- 2 trials did not collect contemporaneous data for the control and intervention sites
- 5 measured non-eligible outcomes
- 1 trial included refugees as study participants
- 2 studies used a non-experimental approach (modelling)
- 1 RCT had a randomized allocation of the intervention that was not acceptable
- 2 studies had an IRS coverage under 60%
- 1 trial experienced a population movement of over 10%
- 1 trial sprayed with DDT in an area with documented DDT resistant *Anopheles.*

Risk of bias in included studies

For an overview of the risk of bias see Figure 1 and Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

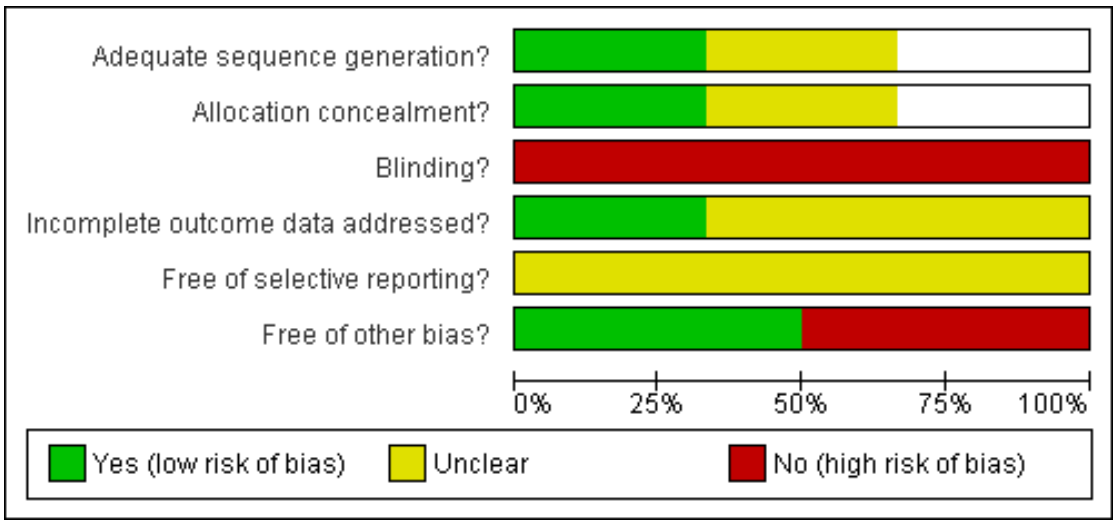
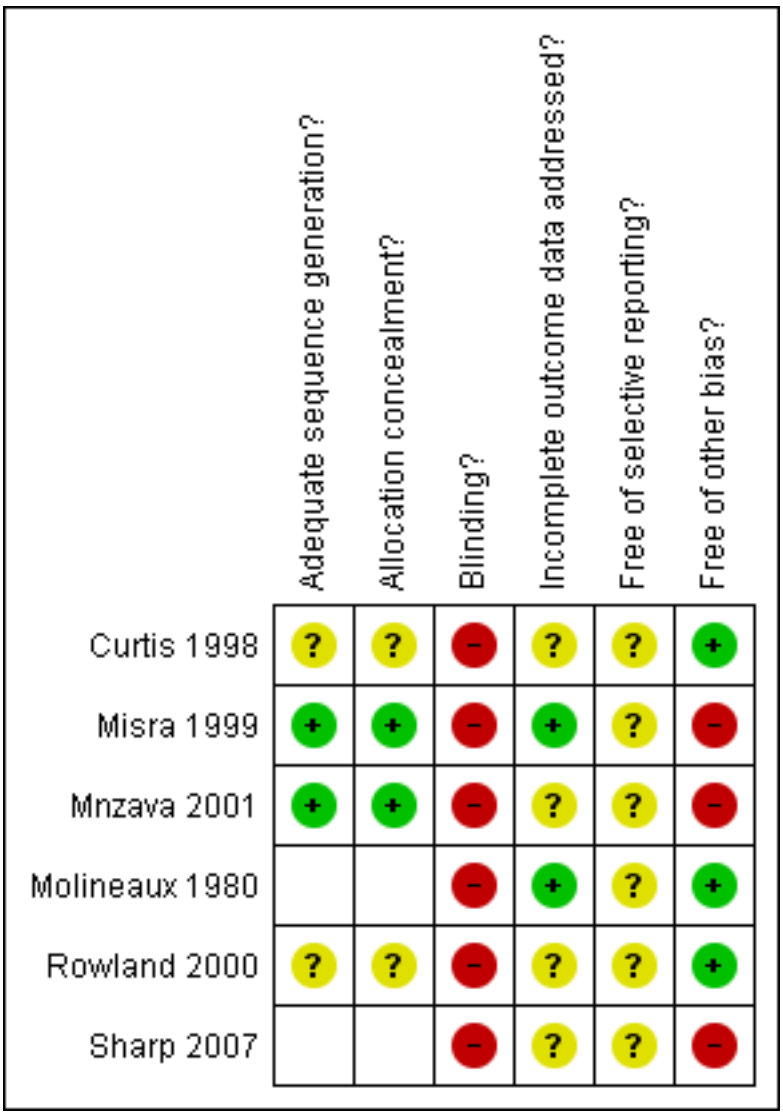


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Two of the four RCTs (Misra 1999; Mnzava 2001) generated allocation sequences by public drawing/tossing of coins. The risk of bias with these methods is low and allocation concealment is ensured by the fact that the allocation was made in public. The remaining two RCTs (Curtis 1998; Rowland 2000) don't specify how the randomization was done and how allocation concealment was secured. Therefore the risk for bias can't be assessed.

Blinding

Blinding is neither possible for IRS nor for ITNs and this criteria should therefore not be considered for assessing study quality. Given the type of interventions and the nature of the outcomes, the risk of bias resulting from the absence of blinding is judged as low.

Incomplete outcome data

Two of the six included trials (Misra 1999; Molineaux 1980) reported changes in the number of participants over time. In one trial (Misra 1999) the losses to follow-up were under 10% and therefore the risk of bias was considered to be low. In one other trial (Molineaux 1980), there was a large migration with 15% to 20% of the population changing per year. The migration was described in detail within the study. Furthermore, the study did an analysis to check for the risk of bias due to the population movements and it was considered to be low.

The other trials didn't report on losses to follow-up. Since they were calculating "person-time-at-risk" as denominators the rates were accurate but the risk of selection bias over time could not be estimated.

Selective reporting

None of the studies contained enough information to permit a reliable judgment of the risk of this type of bias.

Other potential sources of bias

In one trial (ITS, Sharp 2007) all age categories were sampled in December 1999, but subsequent surveys were confined to children two to 14 years of age. Fortunately the authors gave details by age in the 1999 survey and hence this change did not matter.

Mnzava 2001 compared IRS versus ITNs. However, houses in bed net blocks had already been sprayed by the time the nets were distributed in 2007. Even though there was immediately an effort by investigators to re-plaster these houses to cover the insecticide on the walls, the effect of ITNs might be overestimated due to the dual protection for a limited time. In subsequent years, house spraying was deliberately withdrawn in blocks with bed nets.

In the study of Misra 1999 a high incidence of plastering mud on the walls of houses was reported (Misra 1999). This most likely reduced the effectiveness of IRS and hence underestimated its real effect. Unfortunately the authors don't provide detailed data on the replastering to allow a judgment on its impact.

Effects of interventions

Comparison 1: IRS versus no IRS

Stable malaria (EIR > 1)

Incidence of infection: Only one RCT assessed the impact of IRS against no IRS in a stable malaria setting: Curtis 1998 compared the impact of IRS with lambdacyhalothrin versus a control group with no intervention in a highly endemic malaria setting in Tanzania. In that trial IRS was shown to be effective in protecting children aged less than five years from reinfection with malaria parasites following radical cure: over an 11 month period, the PE was 54% (Table 4). In the same setting, malaria case incidence assessed by passive surveillance was probably reduced in children aged one to five years: PE 14%, but not in children older than five years: PE -2% (Table 4).

One CBA in Nigeria (Molineaux 1980) and one ITS in Mozambique (Sharp 2007) were also conducted in stable malaria settings but neither of these two trials measured incidence rates. However, Molineaux 1980 measured infant parasitological conversion rates and found a slight reduction in the areas with IRS compared to areas without (Table 5).

Prevalence of infection: For malaria prevalence no difference was seen between the IRS and control groups in the RCT of Curtis 1998 : PE 6% (Table 4). In both Molineaux 1980 and Sharp 2007 the malaria prevalence was reduced where IRS was applied. However, Molineaux 1980 found a significant difference only for the prevalence rates during the wet season in which IRS showed a PE of 26% (95% CI 20 to 32%), while the PE in the dry season was only 6% (95% CI -4 to 15%) (Table 6). In Mozambique (Sharp 2007), the prevalence rate dropped from 60 to 65% before the spraying to 4% in 2005 (Table 7). On average the prevalence rate was 62% before spraying (939/1515) and 16% (638/3960) after, a reduction of 74%.

Anaemia: In Curtis 1998, the haemoglobin levels were significantly lower in the control group than in the IRS group (mean difference (MD) 0.85 g/dL; Table 8).

Infant mortality rate: Molineaux 1980 measured infant mortality rates (IMR) but unfortunately without measuring it in a control area. They then derived evidence of impact from the close correlation between reduced infant parasitological conversion rates and IMR. It is unfortunate that because of this limitation these unique mortality data could not be used in our analysis.

Unstable malaria (EIR < 1)

Incidence of infection: IRS was shown to significantly reduce the incidence of malaria infections with a PE of 31% in India (Misra 1999) and 88% (95% CI 69 to 96%) in Pakistan (Rowland 2000; Table 9). IRS also reduced the incidence of malaria in a similar way when looking separately at *P. falciparum* (PE 93%, 95% CI 61 to 98% in Pakistan) and *P. vivax (*PE 79%, 95% CI 45 to 90% in Pakistan).

Prevalence of infection: In both India (Misra 1999) and Pakistan (Rowland 2000) there was an impact of IRS on malaria prevalence, when any infection was considered: PE 28% in India and PE 76% in Pakistan (Table 9).

For *P. falciparum* only, there was a reduction in prevalence in both India (PE 34%) and Pakistan (PE 92%)(Table 9).

For *P. vivax* only, there was no impact in India (PE -2%) while there was a significant PE of 68% in Pakistan (Table 9).

Comparison 2: IRS versus Insecticide Treated Nets (ITNs)

Stable malaria (EIR > 1)

Incidence of infection: only one RCT was done in an area of stable transmission (Curtis 1998). When comparing parasitological re-infection rates after radical cure in short-term cohorts, ITNs had a tendency for a greater protective effect than IRS in that Tanzanian trial (risk ratio IRS:ITN = 1.22, CI not adjusted for clustering) (Table 10).

When the incidence rate of malaria episodes was measured by passive case detection, there was no difference detectable in children aged one to five years: risk ratio 0.88 (upper unadjusted CI approached 1). No difference was seen for children older than five years: risk ratio 0.98 (Table 10).

Prevalence of infection: In Curtis 1998 prevalence rates were found to be no different within the IRS and ITN groups: risk ratio 1.06 (Table 10).

No difference in haemoglobin levels were detected either: MD 0.06 g/dL (Table 8).

Unstable malaria (EIR < 1)

Incidence of infection: Misra 1999 found a significant difference between IRS and ITNs: risk ratio IRS:ITN = 1.48 (95% CI 1.37 to 1.60), but Mnzava 2001 did not because the 95% CI were large: risk ratio 1.34 (cluster unadjusted CI 95% 0.77 to 2.70) (Table 11).

Prevalence of infection: only one trial in India (Misra 1999) compared IRS to ITNs for this outcome. ITNs appeared to give a better protection against any infection compared to IRS: risk ratio IRS:ITN = 1.70, but CIs were not adjusted (Table 11). The point estimates of this apparent difference were similar for *P. falciparum* infections: risk ratio IRS:ITN 1.78 and slightly lower for *P. vivax* infections: risk ratio 1.37.

India (Misra 1999) and KwaZulu Natal (Mnzava 2001) have a long history of IRS with 50 years and 60 years of spraying, respectively. The effect such a long pre-trial spraying period had on the measures of impact, especially for the ITN arm, could not be explored in the present analysis.

DISCUSSION

Since the 1950s, IRS has been used widely in many areas of the world, especially in Asia, Latin America and Southern Africa. IRS with DDT and other insecticides has been one of the main interventions leading to the elimination of malaria in about half of the world's regions, for example in much of southern Europe, North America, Japan, Central Asia and Latin America and it is still being widely used (Lengeler 2003;WHO 2008). Very low levels of malaria transmission have also been achieved and maintained in countries as different as India, Tadjikistan and Colombia. Hence the effectiveness of this intervention is beyond doubt. Unfortunately, the epidemiological effect has never been quantified properly, so that a comparison with other malaria control interventions, for example with ITNs, is impossible. As a result, an accurate comparative cost-effectiveness assessment is also impossible.

With the exception of Southern Africa (South Africa, Namibia, Botswana, Swaziland, and Zimbabwe) and the Ethiopian and Madagascar highlands, the implementation of IRS in the highly endemic areas of sub-Saharan Africa has been restricted in geographical extent and usually only undertaken for a limited time period. Recently, IRS was introduced in a number of African countries - southern Mozambique, Equatorial Guinea, Zambia, Ghana, Sao Tome, and Zanzibar. There is a new interest for IRS since 2007 in the wake of the United States President's Malaria Initiative (PMI). For many of the other endemic countries of sub-Saharan Africa, vector control has been scaled up since 2000 onwards through the increased deployment of ITNs. In this context, two important questions have emerged: (1) what are the comparative advantages, including feasibility, cost and impact of ITNs and IRS; and (2) is there any benefit in combining both IRS and ITNs together to increase impact, especially in view of the goal of malaria elimination declared in 2007?

While there are now good data on comparative feasibility and cost (see review by Yukich 2008), the present review confirms the paucity of high-quality evidence in the comparative assessment of health impact. There are too few high-quality randomized controlled studies on the health effects of IRS, and not enough geographical coverage. Only six out of 134 identified studies met our inclusion criteria (four RCTs, one CBA and one ITS) and not all key malariological outcomes were addressed within these studies. Unfortunately, none of the studies investigated the potential of IRS for reducing child mortality rates. In some ways, these results are not entirely surprising considering the fact that (1) IRS started to be implemented on a large scale after the invention of DDT in 1943 (and hence before the first RCT conducted in 1948), and (2) IRS with DDT was outstanding in its health effects from the start, therefore giving no strong rationale for public health officials in the 1950s and 1960s to formally test its effects.

Currently, our evidence on the question of the impact of the combination of IRS with ITNs is also very limited. A recent review (Kleinschmidt 2009) has suggested some additive effects but the evidence only stems from descriptive studies, and properly conducted RCTs are urgently required.

Overall, the formal quality of the six included trials was considered to be satisfactory. Two of the four RCTs used appropriate methods for sequence generation and allocation concealment, whereas the other two trials didn't mention their procedure. However, given the nature of the intervention and the fact that it was allocated by cluster, this is unlikely to have led to bias in the results. Due to the nature of the intervention, blinding was not possible, but no risk of bias was expected because of this.

A much bigger issue for the validity of the results is the implementation of the interventions.In three (Misra 1999;Mnzava 2001;

Rowland 2000) of the four RCTs, the control and/or ITN arms of the trials had a long previous history of IRS, and spraying was simply suspended in the ITN arm for the duration of the trial. Obviously, the entomological baseline situation was not any more that of an untouched area. In addition, insecticide was sprayed shortly before ITN distribution in the ITN arms in India and Tanzania. Despite the best efforts by investigators to minimize the effects of this by re-plastering the walls, that interference is still likely to have had an independent effect on the outcomes. Unfortunately, it is impossible to quantify these effects.

Only two different classes of insecticides (carbamates and pyrethroids) were used in the reviewed trials, to which the mosquitoes were fully susceptible in all settings. Insecticide resistance is an obvious threat to the effectiveness of IRS. However, unlike 50 years ago, when DDT was the only insecticide on hand, there are now 12 different insecticides within four different chemical classes available for IRS. This gives the possibility to alternate the insecticides and to switch to other insecticides in case of emerging resistance. This is a clear advantage over ITNs, for which only one class of insecticide is available (pyrethroids). On the other hand, ITNs still offer a physical barrier to the vector, even if the insecticide doesn't work anymore, whereas for IRS the protection through the insecticide will be strongly reduced.

The low number of trials unfortunately prevented us from carrying out any form of sub-group analysis, which would have included the impact of different types of insecticides, the length of the transmission season, the type of vectorial systems and other factors thought to be important.

The four included randomized controlled trials were distributed between Asia and sub-Saharan Africa. Only one RCT was done in a stable malaria setting (EIR >1, Curtis 1998). Three RCTs were done in unstable malaria settings (EIR <1). Two of them were in Asia (Misra 1999 (India); Rowland 2000 (Pakistan)) and one in Africa (Mnzava 2001 (South Africa)).

Comparing IRS to no IRS in stable settings, in the study in Tanzania (Curtis 1998) the risk for children under six to get re-infected with malaria parasites after radical cure was reduced approximately by half (PE: 54%), an indication that IRS reduced malaria transmission. Paradoxically, no changes was observed in malaria incidence rates when cases were detected by passive surveillance (without initial parasite clearance). Possibly, the clearance of all infections with an effective antimalarial (chlorproguanil-dapsone), something not usually done in vector control trials, had an additional independent effect. Hence, the generalization of these results to other malaria endemic areas needs to be questioned.

For IRS versus no IRS in unstable areas, the trials from India and Pakistan both showed that IRS protected all age groups and for both *P. falciparum* and *P. vivax* in these settings from malaria infections.

When comparing IRS versus ITNs, in the one trial in a stable area Curtis 1998 there was a trend towards ITNs having a greater PE than IRS on incidence after radical cure but the unadjusted CIs approached 1 (risk ratio IRS:ITN = 1.22). However, when the incidence was measured by passive case detection, there was a slight but non significant difference in favour of IRS in children aged one to five years (risk ratio = 0.88). No difference was found for malaria prevalence or haemoglobin.

ITN appeared to be more protective than IRS in unstable areas. For malaria prevalence, ITNs appeared to give better protection against any infection compared to IRS in India.

The results of this review do not reconcile well with the impressive historical reductions of malaria in many areas of the world following the introduction of IRS. Among these areas were also a number of high transmission areas in sub-Saharan Africa (Kouznetsov 1977;Mabaso 2004). In part this discrepancy could be explained by the fact that programmes were conducted on a much larger scale and for a much longer time period than trials, with a resulting better impact. Hence,**the lack of positive evidence from formal trials should not, in the case of IRS, be interpreted as a lack of effect of the intervention**. Rather, it is the consequence of a lack of high-quality and long-duration trials on a large scale done in areas not previously under vector control. As a result, the main aim of the review (to quantify the health effects of IRS) could not be achieved and our major conclusion is that high-quality evidence from RCTs is still required. For obvious ethical reasons a control group without vector control intervention is not acceptable any more and such trials should therefore have at least two arms, an IRS arm and an ITN arm. Given the importance of also assessing the combined effect of IRS and ITNs, a third arm with both interventions together would be highly desirable.

AUTHORS' CONCLUSIONS

Implications for practice

- The current evidence is insufficient to quantify properly the effect of IRS in high transmission settings although it seems clear that IRS leads to health benefits.

- Available good quality evidence confirms that IRS works in reducing malaria in unstable malaria settings.

- At present, a quantitative epidemiological comparison between IRS and ITNs is not possible.

- No trial investigated the effect of IRS in reducing (child) mortality.

- There is insufficient epidemiological evidence to assess the effect of other determinants of impact, such as the insecticide class used for IRS, the type of transmission, the dominant vector species and socio-cultural determinants.

Implications for research

- There is an urgent need for more RCTs comparing IRS with ITNs in a number of settings with different epidemiological and socio-cultural characteristics.

- Ideally future trials should try and evaluate the effect of IRS in areas with no previous history of malaria control activities.

- Ideally, such RCTs should have a third arm with a combination of high coverage IRS with high coverage ITNs; each arm should at least have 3 to 5 large-size clusters.

- Participants of all age-groups should be included in such trials.

ACKNOWLEDGEMENTS

The protocol development and conduct of the review received funding from the Swiss Tropical and Public Health Institute and the United States Agency for International Development (USAID) through Research Triangle Institute (RTI). Views expressed in this publication do not necessarily reflect the views of the USAID or the United States Government.

The editorial base of the Cochrane Infectious Diseases Group is funded by the UK Department for International Development (DFID) for the benefit of developing countries.

We thank Sarah Donegan for providing statistical support, Lois Orton for reorganising the tables, and The Cochrane Infectious Diseases Group editorial base (especially Anne-Marie Stephani) for final editing . The constructive comments from the five reviewers and from the Editor Patricia Graves were also much appreciated.

We furthermore thank Andrew Beljaev for translating the abstracts of Russian papers and Dominique Guinot for translating a Portuguese paper. Further thanks to Shiva Murugasampillay, Socrates Litsios, José A. Nájera, Raman Velayudhan, Musawenkosi Mabaso and Allan Schapira for providing materials and advice.

REFERENCES

References to studies included in this review

Curtis 1998 ***{published data only}***

Curtis CF. Royal Society of Tropical Medicine and Hygiene Meeting at Manson House, London, 21 January 1999 - Malaria control: bednets or spraying? Background trial in Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999;**93**(5):453–4.

* Curtis CF, Maxwell CA, Finch RJ, Njunwa KJ. A comparison of use of a pyrethroid either for house spraying or for bednet treatment against malaria vectors. Tropical Medicine & International Health 1998; Vol. 3, issue 8: 619–31.

Misra 1999 ***{published data only}***

Bhatia MR, Fox-Rushby J, Mills A. Cost-effectiveness of malaria control interventions when malaria mortality is low: insecticide-treated nets versus in-house residual spraying in India. *Social Science & Medicine* 2004;**59**(3):525–39.

* Misra SP. *Indoor residual spray versus treated mosquito nets using deltamethrin to control malaria - a community randomized trial in rural Surat, India (PhD thesis)*. London: University of London, 1999.

Misra SP, Webber R, Lines J, Jaffar S, Bradley DJ. Malaria control: bednets or spraying? Spray versus treated nets using deltamethrin--a community randomized trial in India. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999;**93**(5):456–7.

Mnzava 2001 ***{published data only}***

Goodman CA, Mnzava AE, Dlamini SS, Sharp BL, Mthembu DJ, Gumede JK. Comparison of the cost and cost-effectiveness of insecticide-treated bednets and residual house-spraying in KwaZulu-Natal, South Africa. *Tropical Medicine & International Health* 2001;**6**(4):280–95.

Mnazva AE, Dlamini SS, Sharp BL, Mthembu DJ, Gumede K, Kleinschmidt I, et al. Malaria control: bednets or spraying? Trial in Kwazulu-Natal, South Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999; **93**(5):455–6.

* Mnzava AE, Sharp BL, Mthembu DJ, le Sueur D, Dlamini SS, Gumede JK, et al. Malaria control--two years' use of insecticide-treated bednets compared with insecticide house spraying in KwaZulu-Natal. South African Medical Journal 2001; Vol. 91, issue 11:978–83.

Molineaux 1980 ***{published data only}***

Molineaux L, Gramiccia G. *The Garki Project. Research on the Epidemiology and Control of Malaria in the Sudan Savanna of West Africa*. Geneva: World Health Organization, 1980.

Rowland 2000 ***{published data only}***

Rowland M, Mahmood P, Iqbal J, Carneiro I, Chavasse D. Indoor residual spraying with alphacypermethrin controls malaria in Pakistan: a community-randomized trial. *Tropical Medicine & International Health* 2000;**5**(7): 472–481.

Sharp 2007 *{published data only}*
Sharp BL, Kleinschmidt I, Streat E, Maharaj R, Barnes KI, Durrheim DN, et al. Seven years of regional malaria control collaboration--Mozambique, South Africa, and Swaziland. *American Journal of Tropical Medicine and Hygiene* 2007;**76** (1):42–7.

References to studies excluded from this review

Afifi 1959 *{published data only}*
Afifi SED. Malaria eradication pilot projects with special reference to Saudi Arabia (EM/ME-Tech.2/11). Second Regional Conference on Malaria Eradication;1959 Nov 16-21; Addis Ababa. Geneva: World Health Organization, 1959.

Afridi 1947 *{published data only}*
Afridi MK, Bhatia ML. Malaria control of villages around Quetta (Baluchistan) with D.D.T. *Indian Journal of Malariology* 1947;**1**(2):279–87.

Alves 1953 *{published data only}*
Alves W, Blair DM. An experiment in the control of malaria and bilharziasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1953;**47**(4):299–308.

Andrews 1951 *{published data only}*
Andrews JM. Nation-wide malaria eradication projects in the Americas. I. The eradication program in the U.S.A. *Journal. National Malaria Society* 1951;**10**(2):99–123.

Ansari 1986 *{published data only}*
Ansari MA, Sharma VP, Batra CP, Razdan RK, Mittal PK. Village scale trial of the impact of deltamethrin (K-othrine) spraying in areas with DDT and HCH resistant Anopheles culicifacies. Indian Journal of Malariology 1986; Vol. 23, issue 2:127–31.

Ansari 1990 *{published data only}*
Ansari MA, Sharma VP, Razdan RK, Mittal PK. Field evaluation of deltamethrin against resistant Anopheles culicifacies in Distt. Ghaziabad (U.P.) India. Indian Journal of Malariology 1990; Vol. 27, issue 1:1–13.

Ansari 2004a *{published data only}*
Ansari MA, Razdan RK. Impact of residual spraying of bendiocarb against the malaria vector Anopheles culicifacies in selected villages of the Ghaziabad District, Uttar Pradesh, India. *Journal of the American Mosquito Control Association* 2004;**20**(4):418–23.

Ansari 2004b *{published data only}*
Ansari MA, Razdan RK. Follow-up studies after withdrawal of deltamethrin spraying against Anopheles culicifacies and malaria incidence. *Journal of the American Mosquito Control Association* 2004;**20**(4):424–8.

Arredondo-Jimenez 1993a *{published data only}*
Arredondo-Jimenez JI, Loyola EG, Rodriguez MH, Danislozano R, Fuentes G, Villarreal C. Effectiveness of A Low-Volume Carbamate Insecticide for Malaria Control. *Salud Publica de Mexico* 1993;**35**(1):27–38.

Arredondo-Jimenez 1993b *{published data only}*
Arredondo-Jimenez JI, Rodriguez MH, Bown DN, Loyola EG. Indoor low-volume insecticide spray for the control of Anopheles albimanus in southern Mexico. Village-scale trials of bendiocarb, deltamethrin and cyfluthrin. *Journal of the American Mosquito Control Association* 1993;**9**(2): 210–20.

Barai 1982 *{published data only}*
Barai D, Hyma B, Ramesh A. The scope and limitations of insecticide spraying in rural vector control programmes in the states of Karnataka and Tamil Nadu in India. Ecology of Disease 1982; Vol. 1, issue 4:243–55.

Barutwanayo 1991 *{published data only}*
Barutwanayo M, Coosemans M, Delacollette C, Bisore S, Mpitabakana P, Seruzingo D. Campaign against malaria vectors in the framework of a rural development project in Burundi. *Annales de la Société Belge de Médecine Tropicale* 1991;**71 Suppl 1**:113–25.

Bhatnagar 1974 *{published data only}*
Bhatnagar VN Wattal BL, Sharma KL, Joshi GC, Mathur PS. Field trials with Fenitrothion* [0,0-dimethyl 0-(4-nitro-m-tylol) phosporothioate] against DDT resistant *Anopheles culicifacies* in Siliser Area, District Alwar, Rajasthan. *Journal of Communicable Diseases* 1974;**6**(4):241–55.

Bradley 1991 *{published data only}*
Bradley DJ. Morbidity and mortality at Pare-Taveta, Kenya and Tanzania, 1954-66: The effects of a period of malaria control. *Disease and Mortality in Sub-Saharan Africa*. Oxford: Oxford University Press for the World Bank, 1991: 248–63.

Brieger 1996 *{published data only}*
Brieger WR, Onyido AE, Sexton JD, Ezike VI, Breman JG, Ekanem OJ. Monitoring community response to malaria control using insecticide-impregnated bed nets, curtains and residual spray at Nsukka, Nigeria. Health Education Research 1996; Vol. 11, issue 2:133–45.

Cai 1999 *{published data only}*
Cai X, Si YZ, Liang ZT, Liu J, Wang J, Wang YQ, et al. A comparative study of deltamethrin impregnated mosquito nets and DDT residual spraying for controlling residual malaria foci transmitted by *Anopheles dirus*. *Zhongguo Jishengchongbing Fangzhi Zazhi [Chinese Journal of Parasitic Disease Control]* 1999;**4**(2):86–90.

Cavalié 1961a *{published data only}*
Cavalié Ph, Mouchet J. La campagne experimentale d'eradication du paludisme dans le nord de la republique du cameroun I. Les vecteurs de l' epidemiologie de paludisme dans le Nord-Cameroun. *Médecine Tropicale : revue du Corps de santé colonial* 1961;**21**:846–69.

Cavalié 1961b *{published data only}*
Cavalié Ph, Mouchet J. La campagne experimentale d'eradication du paludisme dans le nord de la republique du cameroun II. Les operations de lutte antipaludique et leurs resultats. World Health Organisation. WHO, 1961.

Charlwood 1995 *{published data only}*
Charlwood JD, Alecrim WD, Fe N, Mangabeira J, Martins VJ. A field trial with Lambda-cyhalothrin (ICON) for the intradomiciliary control of malaria transmitted by

Anopheles darlingi root in Rondonia, Brazil. *Acta Tropica* 1995;**60**(1):3–13.

Conteh 2004 ***{published data only}***
Conteh L, Sharp BL, Streat E, Barreto A, Konar S. The cost and cost-effectiveness of malaria vector control by residual insecticide house-spraying in southern Mozambique: a rural and urban analysis. Tropical Medicine & International Health 2004; Vol. 9, issue 1:125–32.

Coosemans 1978 ***{published data only}***
Coosemans M. [Control of malaria vectors in tropical Africa (author's transl)]. Médecine Tropicale : revue du Corps de santé colonial 1978; Vol. 38, issue 6:679–84.

Coosemans 1989 ***{published data only}***
Coosemans M, Barutwanyo M. Malaria control by antivectorial measures in a zone of chloroquine-resistant malaria: a successful programme in a rice growing area of the Rusizi valley. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1989;**83 Suppl**:97–8.

Coosemans 1991 ***{published data only}***
Coosemans M. [Development of a campaign strategy against malaria in a rice-growing region of Burundi]. Bulletin et Mémoires de l'Académie Royale de Médecine de Belgique 1991; Vol. 146, issue 1–2:157–65.

Coppen 1999 ***{published data only}***
Coppen GDA. The Use of Fendona Alphacypermethrin for residual wall spraying and its effects of vector populations and malaria incidence. Second Multilateral Initiative on Malaria (MIM) Pan-African Conference on Malaria; 1999 Mar 14-19; Durban, South Africa. Bethesda (MD): Fogarty International Center, 1999.

Cot 1999 ***{published data only}***
Cot M, Le Goff G, Rakotondraibe EM, Randiranantenainjatovo JL, Raveloson A, Brutus L. Evaluation of Lambda-Cyhalothrin for house-spraying to control malaria vectors on Madagascar Highlands. Second Multilateral Initiative on Malaria (MIM) Pan-African Conference on Malaria; 1999 Mar 14-19; Durban, South Africa. Bethesda (MD): Fogarty International Center, 1999.

Cot 2001 ***{published data only}***
Cot M, Brutus L, Le Goff G, Rajaonarivelo V, Raveloson A. [The campaign against malaria in central western Madagascar: comparison of lambda-cyhalothrin and DDT house spraying. II--Parasitological and clinical study]. Parasite 2001; Vol. 8, issue 4:309–16.

Cot 2002 ***{published data only}***
Cot M, Brutus L, Pinell V, Ramaroson H, Raveloson A, Rabeson D, et al. Malaria prevention during pregnancy in unstable transmission areas: the highlands of Madagascar. *Tropical Medicine & International Health* 2002;**7**(7):565–72.

Curtis 1999 ***{published data only}***
Curtis C, Misra S, Rowland M. Comparisons of house spraying with insecticide treated bednets in Tanzania, India and Pakistan. Second Multilateral Initiative on Malaria (MIM) Pan-African Conference on Malaria; 1999 Mar 14-19; Durban, South Africa. Bethesda (MD): Fogarty International Center, 1999.

Curtis 2000 ***{published data only}***
Curtis CF, Mnzava AE. Comparison of house spraying and insecticide-treated nets for malaria control. *Bulletin of the World Health Organization* 2000;**78**(12):1389–400.

Dapeng 1996 ***{published data only}***
Dapeng L, Leyuan S, Xili L, Xiance Y. A successful control programme for falciparum malaria in Xinyang, China. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996;**90**(2):100–2.

Das 1987 ***{published data only}***
Das M, Srivastava BN, Rao CK, Thapar BR, Sharma GK. Field trial of the effectiveness of indoor-spraying with pirimiphos-methyl emulsion for malaria control in a tribal area of Phulbani district, Orissa State, India. Medical and Veterinary Entomology 1987; Vol. 1, issue 3:289–95.

de Zulueta 1954 ***{published data only}***
de Zulueta J, Lachance F. Experience with residual spraying of insecticides in the control of A.leucosphyrus-carried malaria in Sarawak. Report of the Malaria conference for the Western Pacific and South-east Asia regions: 1954 November 15-27; Taipei. Geneva: World Health Organization, 1954. [WHO/MAL/116]

de Zulueta 1961 ***{published data only}***
de Zulueta J, Kafuko GW, Cullen JR, Pedersen CK. The results of the first year of a malaria eradication pilot project in northern Kigezi (Uganda). *East African Medical Journal* 1961;**38**(1):1–26.

Deane 1948 ***{published data only}***
Deane LM, Freire EPSerra, Tabosa W, Ledo J. [A aplicação domiciliar de DDT no contrôleda Malária em localidades da Amazônia]. *Revista do Serviço Especial de Saúde Pública (Rio de Janeiro)* 1948;**1**(4):1121–61.

Dhiman 2005 ***{published data only}***
Dhiman RC, Shahi B, Sharma SN, Nanda N, Khargiwarkar VN, Subbarao SK. Persistence of malaria transmission in a tribal area in Maharashtra, India. Current Science 2005; Vol. 88, issue 3:475–8.

Dodge 1965 ***{published data only}***
Dodge JS. *Outdoor malaria transmission in a DDT-sprayed area of western Sokoto, northern Nigeria*. Geneva: World Health Organisation, 1965.

Doke 2000 ***{published data only}***
Doke PP, Sathe RS, Chouhan SP, Bhosale AS. Impact of single round of indoor residual spray with lambda-cyhalotrin 10% WP on Plasmodium falciparum infection in Akola district, Maharashtra State. *Journal of Communicable Diseases* 2000;**32**(3):190–200.

Dowling 1950 ***{published data only}***
Dowling MA. An experiment in the eradication of Malaria in Mauritius. World Health Organisation. Eliel Felix, Government Print, 1950.

Dowling 1951 ***{published data only}***
Dowling MA. An experiment in the eradication of malaria in Mauritius. *Bulletin of the World Health Organization* 1951;**4**(3):443–61.

Eddey 1944 *{published data only}*
Eddea LG. Spray-killing of mosquitoes in houses - a contribution to malaria control on the Gold Coast. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1944;**38**(3):168–88.

Edeson 1957 *{published data only}*
Edeson JFB, Wharton RH, Wilson T, Reid JA. An experiment in the control of rural malaria in Malaya. *The Medical Journal of Malaya* 1957;**12**(1):319–46.

Farid 1954 *{published data only}*
Farid M.A. Ineffectiveness of DDT residual spraying in stopping malaria transmission in the Jordan Valley. *Bulletin of the World Health Organization* 1954;**11**:765–83.

Faye 1992 *{published data only}*
Faye O, Diallo S, Gaye O, Faye O, Mouchet J. [Evaluation of the efficacy of fenitrothion (Sumithion PM40) on vector density and the prevalence of malaria in Pout (Thies, Senegal)]. *Annales de la Société Belge de Médecine Tropicale* 1992;**72**(2):103–12.

Fontaine 1976 *{published data only}*
Fontaine RE, Pull J, Payne D, Pradhan GD, Joshi G, Pearson JA. *Evaluation of fenitrothion (OMS 43) for malaria control in a large-scale epidemiological trial, Kisumu, Kenya*. Geneva: World Health Organization, 1976. [WHO/VBC/76.645]

Fontaine 1978 *{published data only}*
Fontaine RE, Pull JH, Payne D, Pradhan GD, Joshi GP, Pearson JA, et al. Evaluation of fenitrothion for the control of malaria. *Bulletin of the World Health Organization* 1978;**56**(3):445–52.

Gandahusada 1984 *{published data only}*
Gandahusada S, Fleming GA, Sukamto, et al. Malaria control with residual fenitrothion in Central Java, Indonesia: An operational-scale trial using both full and selective coverage treatments. *Bulletin of the World Health Organization* 1984;**62**(5):783–94.

Gill 1997 *{published data only}*
Gill KS, Rahman SJ, Panda R, Kumar K, Katyal R. Extended field trial of deltamethrin WDP for control of malaria at Jagdalpur, Madhya Pradesh, India. *Indian Journal of Malariology* 1997;**34**(4):173–87.

Gunasekaran 2005 *{published data only}*
Gunasekaran K, Sahu SS, Jambulingam P, Das PK. DDT indoor residual spray, still an effective tool to control Anopheles fluviatilis-transmitted Plasmodium falciparum malaria in India. Tropical Medicine & International Health 2005; Vol. 10, issue 2:160–8.

Guyatt 2002 *{published data only}*
Guyatt HL, Corlett SK, Robinson TP, Ochola SA, Snow RW. Malaria prevention in highland Kenya: indoor residual house-spraying vs. insecticide-treated bednets. Tropical Medicine & International Health 2002; Vol. 7, issue 4: 298–303.

Hamon 1954 *{published data only}*
Hamon J, Dufour G. Antimalarial campaign in La Reunion. *Bulletin of the World Health Organization* 1954;**11**(4-5): 525–56.

Hii 1993 *{published data only}*
Hii JL, Kanai L, Foligela A, Kan SK, Burkot TR, Wirtz RA. Impact of permethrin-impregnated mosquito nets compared with DDT house-spraying against malaria transmission by *Anopheles farauti* and *An.punctulatus* in the Solomon Islands. Medical and Veterinary Entomology 1993; Vol. 7, issue 4:333–8.

Ismail 1974 *{published data only}*
Ismail IA, Notananda V, Schepens J. Studies on malaria and responses of *Anopheles balabacensis balabacensis* and *Anopheles minimus* to DDT residual spraying in Thailand. I. Pre-spraying observations. *Acta Tropica* 1974;**31**(2): 129–64.

Ismail 1975 *{published data only}*
Ismail IA, Notananda V, Schepens J. Studies on malaria and responses of *Anopheles balabacensis balabacensis* and *Anopheles minimus* to DDT residual spraying in Thailand. *Acta Tropica* 1975;**32**(3):206–31.

Ismail 1978 *{published data only}*
Ismail IA, Phinichpongse S, Boonrasri P. Responses of *Anopheles minimus* to DDT residual spraying in a cleared forested foothill area in central Thailand. *Acta Tropica* 1978;**35**(1):69–82.

Jaggi 1984 *{published data only}*
Jaggi YP. Effectiveness of DDT spraying in control of malaria in Hazaribagh. *Journal of the Indian Medical Association* 1984;**82**(1):33–4.

Jambou 2001 *{published data only}*
Jambou R, Ranaivo L, Raharimalala L, Randrianaivo J, Rakotomanana F, Modiano D, et al. Malaria in the highlands of Madagascar after five years of indoor house spraying of DDT. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2001;**95**(1):14–8.

Kamolratanakul 2001 *{published data only}*
Kamolratanakul P, Butraporn P, Prasittisuk M, Prasittisuk C, Indaratna K. Cost-effectiveness and sustainability of lambdacyhalothrin-treated mosquito nets in comparison to DDT spraying for malaria control in western Thailand. *American Journal of Tropical Medicine and Hygiene* 2001;**65**(4):279–84.

Kleinschmidt 2006 *{published data only}*
Kleinschmidt I, Sharp B, Benavente LE, Schwabe C, Torrez M, Kuklinski J, et al. Reduction in infection with Plasmodium falciparum one year after the introduction of malaria control interventions on Bioko Island, Equatorial Guinea. *American Journal of Tropical Medicine and Hygiene* 2006;**74**(6):972–8.

Kleinschmidt 2007 *{published data only}*
Kleinschmidt I, Torrez M, Schwabe C, Benavente L, Seocharan I, Jituboh D, et al. Factors influencing the effectiveness of malaria control in Bioko Island, Equatorial

Guinea. *American Journal of Tropical Medicine and Hygiene* 2007;**76**(6):1027–32.

Lambrecht 1952 ***{published data only}***
Lambrecht FL, Chardome M, Peel E. [Residual spraying with DDT in a quadrilateral of 60 Km2 in the plain of the Ruzzi.]. *Anais do Instituto de Medicina Tropical* 1952;**9**(2): 623–42.

Lantoarilala 1998 ***{published data only}***
Lantoarilala J, Ribes GC, Mouchet J. Impact of antivectorial control on malarial morbidity and mortality in a health district of the Madagascar highlands. *Bulletin de la Société de Pathologie Exotique* 1998;**91**(1):87–90.

Maharaj 2005 ***{published data only}***
Maharaj R, Mthembu DJ, Sharp BL. Impact of DDT re-introduction on malaria transmission in KwaZulu-Natal. *South African Medical Journal* 2005;**95**(11):871–4.

Mastbaum 1951 ***{published data only}***
Mastbaum O. Field experiments with D.D.T. emulsion and wettable D.D.T. with special reference to malaria incidence in Swaziland during the transmission season 1949/50. *East African Medical Journal* 1951;**28**(2):67–74.

Matola 1981 ***{published data only}***
Matola YG, Magayuka SA. Malaria in the Pare area of Tanzania. V. Malaria 20 years after the end of residual insecticide spraying. Transactions of the Royal Society of Tropical Medicine and Hygiene 1981; Vol. 75, issue 6.

Metselaar 1954 ***{published data only}***
Metselaar D. The pilot project of residual spraying in Netherlands New Guinea (WHO/MAL/120). Malaria Conference for the Western Pacific and South-East Asia Regions; Second Asian Malaria Conference; 1954 Nov, 15-24; Baguio, Philippines. Geneva: World Health Organization, 1954.

Metselaar 1957 ***{published data only}***
Metselaar D. A pilot project of residual insecticide spraying in Netherlands New Guinea, contribution to the knowledge of holoendemic malaria. Acta Leidensia 1957; Vol. 27: 1–128.

Metselaar 1960 ***{published data only}***
Metselaar D. Relative increase in the prevalence of Plasmodium falciparum some years after the beginning of a house-spraying campaign in Netherlands New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1960;**54**:523–8.

Metselaar 1961 ***{published data only}***
Metselaar D. Seven years' malaria research and residual house spraying in Netherlands New Guinea. *American Journal of Tropical Medicine and Hygiene* 1961;**10**:327–34.

Mnzava 1993 ***{published data only}***
Mnzava AE, Rwegoshora RT, Tanner M, Msuya FH, Curtis CF, Irare SG. The effects of house spraying with DDT or lambda-cyhalothrin against Anopheles arabiensis on measures of malarial morbidity in children in Tanzania. *Acta Tropica* 1993;**54**(2):141–51.

Najera 1965 ***{published data only}***
Najera JA, Shidrawi GR, Gibson FD, Stafford JS. *A large-scale field trial for the evaluation and assessment of malathion as an insecticide for antimalarial work in southern Uganda*. Geneva: World Health Organisation. WHO/MAL/529, 1965.

Najera 1967 ***{published data only}***
Najera JA, Shidrawi GR, Gibson FD, Stafford JS. A large-scale field trial of malathion as an insecticide for antimalarial work in Southern Uganda. *Bulletin of the World Health Organization* 1967;**36**(6):913–35.

Najjar 1959 ***{published data only}***
Najjar AE, Fontaine RE. Dembia pilot project Beghemder Province, Ethiopia (EM/ME-Tech.2/17). Second Regional Conference on Malaria Eradication; 1959 Nov 6-21; Addis Ababa. Geneva: World Health Organization, 1959.

Nalim 1997 ***{published data only}***
Nalim S, Barodji, Widiarti, Widiyastuti U. A field trial with etofenprox (OMS 3002) as a residual insecticide against malaria vectors, in Tanjung Bunga district, east Flores, Indonesia. *Southeast Asian Journal of Tropical Medicine and Public Health* 1997;**28**(4):851–6.

Nasir 1982 ***{published data only}***
Nasir SM, Ahmad N, Shah MA, Azam CM. A large-scale evaluation of pirimiphos-methyl 25% WP during 1980-1981 for malaria control in Pakistan. *Journal of Tropical Medicine and Hygiene* 1982;**85**(6):239–44.

Nguyen 1996 ***{published data only}***
Nguyen TV, Bui DB, Mai VS, Ta VT, Nguyen TQ, Tan N, et al. [Evaluation of malaria vector control measures in central Vietnam (1976-1991)]. *Sante.* 1996;**6**(2):97–101.

Nyarango 2006 ***{published data only}***
Nyarango PM, Gebremeskel T, Mebrahtu G, Mufunda J, Abdulmumini U, Ogbamariam A, et al. A steep decline of malaria morbidity and mortality trends in Eritrea between 2000 and 2004: the effect of combination of control methods. *Malaria Journal* 2006;**5**:33. [DOI : 10.1186/1475–2875–5–33]

Onori 1975 ***{published data only}***
Onori E, Nushin MK, Cullen JE, Yakubi GH, Mohammed K, Christal FA. An epidemiological assessment of the residual effect of DDT on Anopheles hyrcanus sensulato and A. pulcherrimus (Theobold) in the North eastern region of Afghanistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1975;**69**(2):236–42.

Over 2003 ***{published data only}***
Over M, Bakote'e B, Velayudhan R, Wilikai P, Graves PM. *Impregnated nets cannot fully substitute for DDT: Field effectiveness of alternative methods of malaria prevention in Solomon Islands, 1993-99 (World Bank Policy Research Working Paper No.3044)*. Washington: World Bank, 2003.

Over 2004 ***{published data only}***
Over M, Bakote'e B, Velayudhan R, Wilikai P, Graves PM. Impregnated nets or ddt residual spraying? Field effectiveness of malaria prevention techniques in Solomon

islands, 1993-1999. *American Journal of Tropical Medicine and Hygiene* 2004;**71**(2 Suppl):214–23.

Pampana 1950 ***{published data only}***
Pampana EJ. Large-scale malaria control campaigns using residual insecticides. World Health Organization. World Health Organization, 1950; Vol. WHO/Mal/46.

Pardo 2006 ***{published data only}***
Pardo G, Descalzo MA, Molina L, Custodio E, Lwanga M, Mangue C, et al. Impact of different strategies to control Plasmodium infection and anaemia on the island of Bioko (Equatorial Guinea). *Malaria Journal* 2006;**5**:10. DOI: 10.1186/1475-2875-5-10

Pattanayak 1980 ***{published data only}***
Pattanayak S, Samnotra KG, Seni A. A comparison, on a village scale, of the effect of pirimiphos-methyl and DDT on Anopheles balabacensis - vectored malaria. *Journal of Tropical Medicine and Hygiene* 1980;**83**(5):211–21.

Payne 1976 ***{published data only}***
Payne D, Grab B, Fontaine RE, Hempel JH. Impact of control measures on malaria transmission and general mortality. *Bulletin of the World Health Organization* 1976; **54**:369–77.

Pletsch 1954 ***{published data only}***
Pletsch DJ, Demos EA. Selective spraying of premises in the control of minimus-transmitted malaria in Taiwan (WHO/MAL/107). Malaria conference for the Western Pacific and South-east Asia regions, (Second Asian Malaria conference): 1954 Nov 15-27; Baguio, Philippines. Geneva: World Health Organization, 1954.

Protopopoff 2008 ***{published data only}***
Protopopoff N, Bortel van W, Marcotty T, Herp van M, Maes P, Baza D, et al. Spatial targeted vector control is able to reduce malaria prevalence in the Brundian highlands. *American Journal of Tropical Medicine and Hygiene* 2008;**79** (1):12–8.

Pujara 1983 ***{published data only}***
Pujara PK, Samnotra KG. The impact of fenitrothion (Oms-431) spraying on malaria prevalence in an area of India with Anopheles-culicifacies resistant to DDT, lindane and malathion. *Mosquito News* 1983;**43**(4):484–9.

Rachou 1966 ***{published data only}***
Rachou RG, Schinazi LA, Moura-Lima M. Preliminary note on the epidemiological studies made in El Salvador to determine the causes of the failure of residual spraying to interrupt the transmission of malaria. *Revista Brasileira de Malariologia e Doenças Tropicais* 1966;**18**(3):763–79.

Rafi 1954 ***{published data only}***
Rafi SM. Evaluation of 1st year of extensive spraying operations in the Punjab during 1952. *Pakistan Journal of Health* 1954;**3**(4):227–40.

Rajendram 1951 ***{published data only}***
Rajendram S, Jayewickreme SH. Malaria in Ceylon. Part II. The control of endemic malaria at Anuradhapura by the residual spraying of houses with D.D.T. *Indian Journal of Malariology* 1951;**5**(1):75–124.

Rajendram 1951a ***{published data only}***
Rajendram S, Jayewickreme SH. Malaria in Ceylon. Part I. The control and prevention of epidemic malaria by the residual spraying of houses with D.D.T. *Indian Journal of Malariology* 1951;**5**(1):1–73.

Rakotomanana 2001 ***{published data only}***
Rakotomanana F, Jeanne I, Duchemin JB, Pietra V, Raharimalala L, Tombo ML, et al. [Geographic approach in malaria control in the central highlands of Madagascar]. *Archives de l'Institut Pasteur de Madagascar* 2001;**67**(1-2): 27–30.

Reisen 1993 ***{published data only}***
Reisen WK, Pradhan SP, Shrestha JP, Shrestha SL, Vaidya RG, Shrestha JD. Anopheline mosquito (Diptera: Culicidae) ecology in relation to malaria transmission in the inner and outer terai of Nepal, 1987-1989. *Journal of Medical Entomology* 1993;**30**(4):664–82.

Rodriguez 1994 ***{published data only}***
Rodriguez Lopez MH, Loyola Elizondo EG, Betanzos Reyes AF, Villarreal Trevino C, Bown DN. [The focal control of malaria. Focal treatment using chemoprophylaxis and home insecticide spraying for the control of malaria in southern Mexico]. *Gaceta Médica de México* 1994;**130**(5):313–9.

Rodríguez 1993 ***{published data only}***
Rodríguez López MH, Loyola Elizondo EG, Betanzos Reyes AF, Villarreal Treviño C, Bown DN. The focal control of malaria. Focal treatment using chemoprophylaxis and home insecticide spraying for the control of malaria in southern Mexico [Control focal del paludismo]. *Gaceta Médica de México* 1993;**130**(5):313–19.

Romi 2002 ***{published data only}***
Romi R, Razaiarimanga MC, Raharimanga R, Rakotondraibe EM, Ranaivo LH, Pietra V, et al. Impact of the malaria control campaign (1993-1998) in the highlands of Madagascar: parasitological and entomological data. American Journal of Tropical Medicine and Hygiene 2002; Vol. 66, issue 1:2–6.

Rowland 1994 ***{published data only}***
Rowland M, Hewitt S, Durrani N. Prevalence of malaria in Afghan refugee villages in Pakistan sprayed with lambdacyhalothrin or malathion. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;**88(4)**:378–9.

Rowland 1997 ***{published data only}***
Rowland M, Hewitt S, Durrani N, Bano N, Wirtz R. Transmission and control of vivax malaria in Afghan refugee settlements in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1997;**91(3)**:252–5.

Russel 1939 ***{published data only}***
Russel Paul F, Knipe Fred W. Malaria control by spray-killing adult mosquitoes: First season's results. *Jounal of the Malaria Institute of India* 1939;**2**:229–37.

Russel 1942 ***{published data only}***
Russel Paul F, Knipe Fred W, Sitapathy NR. Malaria control by spray-killing adult mosquitoes: Fourth season's results. *Jounal of the Malaria Institute of India* 1942;**5**(59):59–76.

Sahondra 2001 *{published data only}*
Sahondra Harisoa LJ, Pietra V, Tombo ML, Albonico M, Ranaivo LH, De Giorgi F, et al. [Epidemiologic surveillance system and control of malaria in the central highlands of Madagascar: results 1999-2000]. Archives de l'Institut Pasteur de Madagascar 2001; Vol. 67, issue 1–2.

Sahu 1993 *{published data only}*
Sahu SS, Gunasekaran K, Sadanandane C. A note on the impact of mud plastering on the efficacy of DDT residual spraying in tribal villages of Koraput District, Orissa State. *Journal of Communicable Diseases* 1993;**25**(2):47–51.

Sahu 1995 *{published data only}*
Sahu SS, Patra KP. A study on insecticide resistance in Anopheles fluviatilis and anopheles culicifacies to HCH and DDT in the Malkangiri district of Orissa. Indian Journal of Malariology 1995; Vol. 32, issue 3:112–8.

Saliternik 1977 *{published data only}*
Saliternik Z. Specific vector control methods for prevention and eradication of malaria in Israel. Tropical and Geographical Medicine 1977; Vol. 29, issue 1:1–7.

Sastry 1961 *{published data only}*
Sastry SH, Rao AR, Rao TS, Sitaraman NL, Achuthan C. A note on the interruption of spraying of residual insecticides in some villages of Visvesvaraya Canal area, Mandya District, Mysore State. Indian Journal of Malariology 1961; Vol. 15:233–8.

Sexton 1994 *{published data only}*
Sexton JD, Breman JG, Ezike VI, Roberts JM, Onyido AE, Beach RF, et al. Comparison of insecticide impregnated bed-nets and curtains and residual house-spraying for malaria control in eastern Nigeria - results after 18 months (abstract). American Journal of Tropical Medicine. 43rd Annual Meeting of American Society of Tropical Medicine and Hygiene, 1994; Vol. 51, issue Suppl.:236.

Sharma 1982 *{published data only}*
Sharma VP, Uprety HC, Nanda Nutan, Raina VK, Parida SK, Gupta VK. Impact of DDT spraying on malaria transmission in villages with resistant Anopheles culicifacies. *Indian Journal of Malariology* 1982;**19**:5–12.

Sharma 1985 *{published data only}*
Sharma GK, Das M, Rao CK, Thapar BR, Roy SM, Barkakaty BN, et al. Evaluation of pirimiphos methyl WDP for control of malaria in Tirap district of Arunachal Pradesh. A preliminary report. *Journal of Communicable Diseases* 1985;**17**(1):77–86.

Sharma 1986 *{published data only}*
Sharma VP, Chandrahas RK, Ansari MA, Srivastava PK, Razdan RK, Batra CP, et al. Impact of DDT and HCH spraying on malaria transmission in villages with DDT and HCH resistant Anopheles culicifacies. *Indian Journal of Malariology* 1986;**23**(1):27–38.

Sharma 1996 *{published data only}*
Sharma DN, Joshi RD, Srivastava PK, Yadava RL, Sadanand AV, Appavoo NC, et al. Impact of deltamethrin spraying on malaria transmission in Rameshwaram Island, Tamil Nadu State - India. Journal of Communicable Diseases 1996; Vol. 28, issue 1:38–44.

Sharma 2005 *{published data only}*
Sharma SN, Shukla RP, Raghavendra K, Subbarao SK. Impact of DDT spraying on malaria transmission in Bareilly District, Uttar Pradesh, India. *Journal of Vector Borne Diseases* 2005;**42**(2):54–60.

Sharp 2002 *{published data only}*
Sharp B, van Wyk P, Sikasote JB, Banda P, Kleinschmidt I. Malaria control by residual insecticide spraying in Chingola and Chililabombwe, Copperbelt Province, Zambia. Tropical Medicine & International Health 2002; Vol. 7, issue 9:732–6.

Singh 2006 *{published data only}*
Singh N, Shukla MM, Mishra AK, Singh MP, Paliwal JC, Dash AP. Malaria control using indoor residual spraying and larvivorous fish: a case study in Betul, central India. *Tropical Medicine & International Health* 2006;**11**(10):1512–20.

Taylor 1986 *{published data only}*
Taylor P, Govere J, Crees MJ. A field trial of microencapsulated deltamethrin, a synthetic pyrethroid, for malaria control. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1986;**80**(4):537–45.

Tewari 1990 *{published data only}*
Tewari SC, Piruthivi V, Mani TR, Rajendran R, Hiriyan J, Joseph AS, et al. Space-spraying with malathion as a supplementary measure for operational malaria control. *Indian Journal of Medical Research* 1990;**91**:151–8.

Trapido 1946 *{published data only}*
Trapido H. The residual spraying of dwellings with DDT in the control of malaria transmission in Panama, with special reference to Anopheles albimanus. *American Journal of Tropical Medicine* 1946;**26**(4):383–415.

van Thiel 1951 *{published data only}*
van Thiel PH, Winoto RMP. *Summary report on the control of highly endemic malaria, carried by Anopheles sundaicus, by means of DDT house spraying, in a village of Java (Indonesia). (Expert committee on malaria)*. Geneva: World Health Organization, 1951.

van Wyk 2002 *{published data only}*
van Wyk P, Senseta H, Banda P, Sikasote JB. Introduction of DDT for residual spraying for malaria vector control in Copper-belt, Zambia. Third Multilateral Initiative on Malaria (MIM) Pan-African Conference on Malaria; 2002 Nov 17-22; Arusha, Tanzania. Bethesda (MD): Fogarty International Center, 2002.

Verdrager 1975 *{published data only}*
Verdrager J, Arwati. Impact of DDT spraying on malaria transmission in different areas of Java where the vector *A.aconitus* is resistant to DDT. *Health Studies in Indonesia* 1975;**3**(2):29–39.

Viswanathan 1947 *{published data only}*
Viswanathan DK. Control of rural malaria with D.D.T. indoor residual spraying in Kanara and Dharwar districts, Bombay Province. First year's results. *Indian Journal of Malariology* 1947;**1**:487–503.

Viswanathan 1950 *{published data only}*

Viswanathan DK, Gadre SB. Field experiments to determine the relative efficacy in malaria control of different dosage regimens of dichloro-diphenyl-trichloroethane (D. D. T.) as judged by mosquito densities, spleen rates, parasite rates and chemical estimation of the residual deposits of D.D.T. at varying intervals after each application as an indoor spray. *Indian Journal of Malariology* 1950;**4**(4):487–503.

Wattal 1978 *{published data only}*

Wattal BL, Bhatnagar VN, Joshi GC, Ambawani GJ, Patel HN. Fenitrothion* indoor residual spray and its impact on malaria transmission in Garbara-Gujarat. *Journal of Communicable Diseases* 1978;**10**(1):31–40.

WHO 2007 *{published data only}*

World Health Organisation. *Malaria Eradication in Ceylon*. Geneva: World Health Organization, 2007.

Wilson 1954 *{published data only}*

Wilson T. An experiment in rural malaria control in Malaya (WHO/MAL/113). Malaria conference for the Western Pacific and South-East Asia Regions; second Asian Malaria Conference; 1954 Nov 15-34; Baguio, Philippines. Geneva: World Health Organization, 1954.

Wu 1984 *{published data only}*

Wu ZY, Kan SP, Shen YZ, Chen FQ, Lu ZG, Jin TS, et al. [Studies on DDT residual spraying for controlling Anopheles lesteri anthropophagus and Plasmodium falciparum malaria]. *Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi [Journal of Parasitology & Parasitic Diseases]* 1984;**2**(4):220–3.

Wu 1993 *{published data only}*

Wu N, Qin L, Liao G, Zhou W, Geng W, Shi Y, et al. Field evaluation of bednets impregnated with deltamethrin for malaria control. *Southeast Asian Journal of Tropical Medicine and Public Health* 1993;**24**(4):664–71.

Xu 1998 *{published data only}*

Xu B, Xiao X, Webber RH, Lines JD. Comparison of the effect of insecticide-treated bed nets and DDT residual spraying on the prevalence of malaria transmitted by Anopheles anthropophagus in China. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1998;**92**(2): 135–6.

Xu 2002 *{published data only}*

Xu JW, Yang H, Yang ZQ, Yang GC, Ma XW, Wang WR, et al. [Cost-effectiveness analysis of the current measures for malaria prevention in Yuanjiang valley, Yunnan province]. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi [Chinese Journal of Parasitology & Parasitic Diseases]* 2002;**20** (4):238–41.

Zaphiropoulos 1959 *{published data only}*

Zaphiropoulos MA. Objectives and achievements of the WHO malaria pilot project in the Awash valley, Ethiopia: 1956-1959. Second Regional Conference on Malaria Eradication; 1959 Nov 16-21; Addis Ababa. Geneva: World Health Organization, 1959. [EM/ME–Tech.2/6]

References to studies awaiting assessment

Kere 1992 *{published data only}*

Kere JF, Kere NK. Bed-nets or spraying? Cost analyses of malaria control in the Solomon Islands. *Health Policy and Planning* 1992;**7**(4):382–6.

Kere NK. *Permethrin impregnated bednets and DDT residual spraying multicentre comparative trial in Solomon Islands [PhD thesis]*. London: University College London, 1992.

Additional references

Adinarayanan 2007

Adinarayanan S, Critchley J, Das PK, Gelband H. Diethylcarbamazine (DEC)-medicated salt for community-based control of lymphatic filariasis. *Cochrane Database of Systematic Reviews* 2007, Issue 1. DOI: 10.1002/14651858.CD003758.pub2

Bennett 2002

Bennett S, Parpia T, Hayes R, Cousens S. Methods for the analysis of incidence rates in cluster randomized trial. *International Journal of Epidemiology* 2002;**31**:839–846.

Carneiro 2007

Carneiro IA, Drakeley CJ, Owusu-Agyei S, Mbando B, Chandramohan D. Haemoglobin and haematocrit: is the threefold conversion valid for assessing anaemia in malaria-endemic settings?. *Malaria Journal* 2007;**6**(67). DOI: 10.1186/1475-2875-6-67

Curtis 2001

Curtis C, Mnzava A. Treated nets vs house spraying. *Bulletin of the World Health Organization* 2001;**79**(7):687.

EPOC 2002

Cochrane Effective Practice and Organisation of Care Review Group (EPOC). The data collection checklist. www.epoc.uottawa.ca/checklist2002.doc 2002 (accessed 12 May 2007).

Gamble 2006

Gamble C, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. *Cochrane Database of Systematic Reviews* 2006, Issue 2. DOI: 10.1002/14651858.CD003755.pub2

Hargreaves 2000

Hargreaves K, Koekemoer LL, Brooke BD, Hunt RH, Mthembu J, Coetzee M. *Anopheles funestus* resistant to pyrethroid insecticides in South Africa. *Medical and Veterinary Entomology* 2000;**14**(2):181–9.

Hayes 2000

Hayes RJ, Alexander ND, Bennett S, Cousens SN. Design and analysis issues in cluster-randomized trials of interventions against infectious diseases. *Statistical Methods in Medical Research* 2000;**9**(2):95–116.

Higgins 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Kleinschmidt 2009

Kleinschmidt I, Schwabe C, Murugasampilay S, Segura JL, Sima V, Mabunda SJA, et al. Combining indoor residual

spraying and insecticide-treated net interventions. *American Journal of Tropical Medicine and Hygiene* 2009;**81**(3): 519–24.

Kouznetsov 1977
Kouznetsov R. Malaria control by application of indoor residual spraying of residual insecticides in tropical Africa and its impact on community health. *Tropical Doctor* 1977; **7**(2):81–91.

Lengeler 2003
Lengeler, C Sharp B. Indoor residual spraying and insecticide-treated nets. In: Murphy C, Ringheim K, Woldehanna S, Volmink J editor(s). *Reducing malaria's burden: evidence of effectiveness for decision makers*. Washington: Global Health Council, 2003:17–24.

Lengeler 2004
Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database of Systematic Reviews* 2004, Issue 2. DOI: 10.1002/14651858.CD000363.pub2

Mabaso 2004
Mabaso ML, Sharp B, Lengeler C. Historical review of malarial control in southern African with emphasis on the use of indoor residual house-spraying. *Tropical Medicine & International Health* 2004;**9**(8):846–56.

Najera 2001
Najera JA, Zaim M. *Malaria vector control: insecticides for indoor residual spraying [WHO/CDS/WHOPES/2001.3]*. Geneva: World Health Organization, 2001.

RBM 2005
Global Partnership to Roll Back Malaria. *World malaria report: 2005*. Geneva: World Health Organization, 2005.

Review Manager 5 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.0 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Roberts 2004
Roberts D, Curtis C, Tren R, Sharp B, Shiff C, Bate R. Malaria control and public health. *Emerging Infectious Diseases* 2004;**10**(6):1170–1.

Sachs 2002
Sachs J, Malaney P. The economic and social burden of malaria. *Nature* 2002;**415**(6872):680–5.

Schiff 2002
Schiff C. Integrated approach to malaria control. *Clinical Microbiology Reviews* 2002;**15**(2):278–93.

Snow 1999
Snow RW, Craig M, Deichmann U, Marsh K. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bulletin of the World Health Organization* 1999;**77**(8):624–40.

Teklehaimanot 2009
Teklehaimanot HD, Teklehaimanot A, Kiszewski A, Rampao HS, Sachs JD. Malaria in Sao Tome and Principe: on the brink of elimination after three years of effective antimalarial measures. *American Journal of Tropical Medicine and Hygiene* 2009;**80**(1):133–40.

Tseng 2008
Tseng LF, Chang WC, Ferreira MC, Wu CH, Rampao HS, Lien JC. Rapid control of malaria by means of indoor residual spraying of alphacypermethrin in the Democratic Republic of Sao Tome and Principe. *American Journal of Tropical Medicine and Hygiene* 2008;**78**(2):248–50.

WHO 2000
WHO. In: H.M. Gilles, Editor editor(s). *Management of severe malaria: a practical handbook*. 2nd Edition. Geneva: World Health Organization, 2000.

WHO 2006
World Health Organization. Dept. of Communicable Disease Prevention, Control and Eradication. *Pesticides and their application: for the control of vectors and pests of public health importance [WHO/CDS/NTD/WHOPES/ GCDPP/2006.1]*. 6th Edition. Geneva: World Health Organization, 2006.

WHO 2008
World Health Organization. *World Malaria Report 2008*. Geneva: World Health Organization, 2008.

WHOPES 2007
WHO Pesticides Evaluation Scheme (WHOPES). WHO recommended insecticides for indoor residual spraying against malaria vectors. www.who.int/malaria/cmc_upload/ 0/000/012/604/IRSInsecticides.htm (accessed 12 May 2007).

Yukich 2008
Yukich JO, Lengeler C, Tediosi F, Brown N, Mulligan JA, Chavasse D, et al. Costs and consequences of large-scale vector control for malaria. *Malaria Journal* 2008;**7**(258). DOI: 10.1186/1475-2875-7-258

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Curtis 1998

Methods	Study design: cluster randomized controlled trial. Unit of allocation: village. Number of units: 4:4:4 Length of follow-up: prevalence surveys and passive surveillance: 15 months (3rd & 4th quarter 95 to 4th quarter 96). Incidence surveys: 20 months (April 95 to Dec 1996) Incidence of re-infection was monitored once before the interventions and four times after introduction of intervention (once in each quarter of 1996) by taking weekly blood slides. Cross-sectional surveys were carried out monthly from April 1995 to December 1996. In addition, a passive surveillance system was set up. People feeling sick with fever were encouraged to visit a local research assistant, who was taking a blood slide from them, which were collected weekly Different children were used for each cohort. Confidence intervals were not adjusted for clustering. We could retrospectively adjust for the prevalence, but not for the incidence data
Participants	Number of participants: Incidence: 60:60:60 (control:ITNs:IRS), prevalence: 104:93:86, passive surveillance: 500:357:795 Inclusion criteria: incidence: children aged 1 to 6 with cleared pre-existing parasitaemia; prevalence: children aged 1 to 6, passive surveillance: people of all ages feeling sick with fever Exclusion criteria: incidence: children away from home, for having missed the blood slide for more than 1 week; prevalence: children already included in the incidence group, children which were selected in the previous month and children with parasitaemia >4000/μl. Passive surveillance: no specific exclusion criteria mentioned
Interventions	IRS: Microencapsulated lambdacyhalothrin (ICON™) 10%; dosage: 30 mg/m². The wall and roof areas were sprayed with Hudson X-Pert spray pumps. Re-spraying in the villages was carried out seven to eight months after the initial spraying (July to August 1996). The spray coverage was not specifically mentioned but maximal coverage was aimed for ITNs: Lambdacyhalothrin (ICON™); dosage: 10 mg/m² in 2 villages, and 20 mg/m² in the other 2 villages. Retreatment after seven months. The coverage rate was not specifically mentioned
Outcomes	(1) Incidence of re-infection after parasitological clearance with antimalarials (2) Incidence rates by passive case detection (3) Malaria prevalence (4) Haemoglobin levels
Notes	Study location: six villages near Muheza, Tanga Region and six villages near Hale, both in northeast Tanzania EIR: estimated to be above 300 Malaria endemicity: high endemicity with intense perennial transmission

Curtis 1998 (*Continued*)

	Transmission season: April to June Main vector: *Anopheles gambiae*, *Anopheles funestus* and *Anopheles arabiensis* Material of wall sprayed: Mud Insecticide resistance: None (bioassay test showed mortality of 80-100%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Quote: "Random assignment of intervention" Comment: Insufficient information to permit a judgement
Allocation concealment?	Unclear risk	Quote: "Random assignment of intervention" Comment: Insufficient information to permit a judgement
Blinding? Malaria infections	High risk	
Incomplete outcome data addressed? Malaria infections	Unclear risk	The study did not address this outcome
Free of selective reporting?	Unclear risk	There is insufficient information to permit a judgement
Free of other bias?	Low risk	

Misra 1999

Methods	Study design: cluster randomized controlled trial. *Baseline:* Unit of allocation: village. Number of units: 15:15:15. Length of follow-up: two weeks (16th to 30th September 1996) Mass surveys in September 1996 (peak transmission season) in 45 villages within the three ecological zones *Intervention:* Unit of allocation: groups of three nearby villages (but at least one km apart) formed a cluster for random assignment of IRS, ITNs or control). The villages were not evenly distributed within the three ecological zones, 30 in coastal zone, 51 in the plains zone and 45 within the foothill eco zone. The distribution of the randomized villages was equal within the three groups Number of units: 42:42:42. Length of follow-up: 18 months. Active case detection by home visits twice a week by collecting blood smears from all fever cases. On Sundays, treatment was provided to any sick person calling on the health worker. Monitoring from May 1997 until May 1999 (only data collected until 31.12. 1998 were evaluated) Cross-sectional mass surveys once per year within the second half of September in 1997 and 1998 Drop out rates were 6.0% for IRS, 5.2% for ITN and 5.6% for the control group The retrospective adjustment of incidence confidence intervals was not possible. Neither was the adjustment for prevalence data possible
Participants	*Baseline mass survey:* Number of participants: 34,292. No explicit inclusion/exclusion criteria (all ages). *Intervention:* Number of participants: 93,210 (IRS: 30,989; ITNs: 31,168; control: 31,053) No explicit inclusion/exclusion criteria.
Interventions	The first intervention round took place from 26.5. to 14.6.1997; the second round from 23.5 to 14.6.1998 IRS: deltamethrin 2.5% WP; dosage 20 mg/m². Indoor surfaces of the walls, ceiling, back of cupboards, cots, eaves and cattle sheds were sprayed. Overall spray coverage was 92.2% in 1997 and 95.1% in 1998. In 1997 spray coverage was least in the irrigated plain eco zone (87%) and over 95% in the foothill and coastal eco zone. In 1998, coverage was 95% in all 3 zones. 1.36% and 19.3% of the houses which have received IRS were re-plastered after three and six months, respectively ITNs: deltamethrin 2.5% SC; dosage 25 mg/m². Overall net coverage of the whole population was very high, with 99.3% in 1997 and 85.4% in 1998, respectively. Overall, 86.8% of the nets were retreated, with the retreatment taking place one year after the distribution (May 1998). In the irrigated plain eco zone, 88.3% were retreated, whereas 95.7% of the nets in the foothill eco zone were retreated. The coverage rate for the coastal area was not mentioned. Only 4% of the nets were washed after nine months of treatment
Outcomes	(1) Malaria prevalence. (2) Malaria incidence.

Notes	Study location: Surat District in Gujarat State, India. 3.7 million population with 54% distributed in 1281 villages. The district is divided into three ecological zones: (1) Foothill: Eastern tract of hilly land, largely deforested, summer hot and dry, maximal rainfall (2) Irrigated plain: cultivation of paddy, sugar cane and plantains, dam which irrigates the entire plain area (3) Coastal: Western coast belt with sandy soil and heavy industries EIR: <1. Malaria endemicity: coastal area: hypo-endemic; getting hyperendemic towards eastern hilly tracts Transmission season: perennial transmission with peak from June to September Main vector: *Anopheles culicifacies* (zoophilic and endophilic). Material of wall sprayed: mud or cement. Insecticide resistance: *A. culicifacies* is resistant to DDT and malathion, but highly susceptible to deltamethrin, the insecticide used within the study (mortality range for susceptibility tests: 74.4 to 96.5) Net ownership prior to distribution of nets for the trial was significant higher in the IRS group (16.5%) than in the other two groups (ITN:9.5%; control: 15.5%; Chi^2 test= 144.69, df=2, P=0.001)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote:"Public drawing, witnessed by elected leaders, community members, and project government officials" Comment: Valid as randomization procedure.
Allocation concealment?	Low risk	Quote: "Public drawing, witnessed by elected leaders, community members, and project government officials" Comment: As there were many witnesses, the adherence to the randomized allocation is secured
Blinding? Malaria infections	High risk	
Incomplete outcome data addressed? Malaria infections	Low risk	Losses to follow-up: Control: 1750/31053 losses to follow-up (344/31053 due to death; 1215/31053 due to emigration and 191/31053 married and moved away) IRS: 1866/30989 losses to follow-up (319/30989 due to death; 1332/30989 due to emigration and 215/30989 married and moved away) ITN: 1611/31168 losses to follow-up

Misra 1999 (*Continued*)

		(346/31168 due to death; 1034/31168 due to emigration and 231/31168 married and moved away) Additions to the study population: Control: 1035/31053 additions (603/31053 due to birth, 249/31053 due to marriage and 183/31053 due to immigration IRS: 1250/30989 additions (713/30989 due to birth; 305/30989 due to marriage and 232/30989 due to immigration) ITNs: 1424/31168 additions (704/31168 due to birth; 320/31168 due to marriage and 400//31168 due to immigration)
Free of selective reporting?	Unclear risk	There is insufficient information for judgement
Free of other bias?	High risk	Quote: "a high incidence (24.3%) of plastering mud on the walls of houses..." (Bhatia et al. 2004) Comment: the re-plastering of the walls after spraying most likely reduced the effectiveness of IRS

Mnzava 2001

Methods	Study design: cluster paired randomized controlled trial. Unit of allocation: geographical blocks (seven pairs of blocks formed on the basis of their average malaria incidence rate (being as similar as possible within each pair); randomization to ITNs or IRS within each pair Number of units: 7:7 blocks. Length of follow-up: 24 months. Routine active case detection took place monthly by malaria control teams. Blood slides were taken from any member of a household. Passive case detection was done by clinic and hospital staff. Whenever such a case was detected, all household members from where the case came from and including all people living within a 40 km radius of the homestead where the index case occurred, were bled as well. This is the routine procedure for all zones under malaria control in the KwaZulu Natal Province. Calculated incidence rates reflect both passive and active case detection Monitoring from January 1997 to December 1998. But results taken only from 1998 because in 1997 spraying had already taken place in ITN clusters Drop-outs were not taken into account. Confidence intervals were not adjusted for clustering. They could not be adjusted retrospectively (due to matching of the pairs)
Participants	IRS: 7649 ITNs: 5450 No inclusion/exclusion criteria mentioned (all ages).

Mnzava 2001 (*Continued*)

Interventions	IRS: spraying with deltamethrin; dosage 20 mg/m², yearly from September to December, starting in 1996 (prior to the malaria season). The interior walls, ceilings and eaves of all homesteads were sprayed with Hudson X-Pert spray pumps. Spraying coverage is not explicitly mentioned ITNs: distribution of permethrin treated nets in January 1997; target dose 200 mg/m². Annual retreatment in January, using deltamethrin (KO-Tab) in 1998 and permethrin in 1999. Over 90% of the nets were retreated. Usage of ITN in 1997 was 98% and 100% in 1998 Houses in bed net blocks had already been sprayed by the time the nets were distributed in 2007. There was immediately an effort by investigators to re-plaster these houses to cover the insecticide on the walls. In subsequent years, however, house spraying was deliberately withdrawn in blocks with bed nets. Restrict analysis of results to 1998
Outcomes	(1) Malaria incidence (cases per 1000 person-years)
Notes	Study location: homesteads within Ndumu and Makanis areas of Ingwavuma district in KwaZulu Natal Province. 14,000 inhabitants (predominantly Zulus) served by four clinics and one referral hospital. The area has a long history of IRS. Before 1995, it was sprayed with DDT, thereafter there was a switch to deltamethrin EIR: not known but very low because of long-standing malaria control efforts (decades of IRS) Malaria endemicity: not known (annual malaria incidence of 5%) Main vector: *Anopheles arabiensis* (after elimination of *A. funestus* by IRS). Material of wall sprayed: mud and cement. Insecticide resistance: within KwaZulu Natal Province, *A. funestus* was shown to be resistant to deltamethrin (Hargreaves 2000). However, according to Mnzava 2001 there is no evidence that pyrethroid-resistant *A. funestus* occurred in the area during the period of the study. For *A. arabiensis* no resistance was detected in the area.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "Tossing of a coin during community meeting" Comment: Valid as randomization tool
Allocation concealment?	Low risk	Quote: "Tossing of a coin during community meeting" Comment: As there were many witnesses, the adherence to the randomized allocation is secured
Blinding? Malaria infections	High risk	
Incomplete outcome data addressed? Malaria infections	Unclear risk	Quote: "Any population changes over the study period could not be taken into account"

Mnzava 2001 (*Continued*)

Free of selective reporting?	Unclear risk	There is insufficient information to permit a judgement
Free of other bias?	High risk	Houses in bed net blocks had already been sprayed by the time the nets were distributed in 2007. There was immediately an effort by investigators to re-plaster these houses to cover the insecticide on the walls. In subsequent years, however, house spraying was deliberately withdrawn in blocks with bed nets

Molineaux 1980

Methods	Study design: controlled before-and-after study Unit of allocation: village Number of units: 5:6 (control : IRS) Every 10 weeks, house-to-house visits were done and a thick film taken. In case of absence a second visit to the home was done Length of follow-up: 36 months. Drop-out rate unknown, high levels of migration - 15% to 20% per year
Participants	IRS: 2310 Control: 1861 No explicit inclusion/exclusion criteria mentioned (all ages)
Interventions	Propoxur 50% WP; dosage 2 g/m². Three rounds of spraying were applied in 1972, starting on 1 May, 5 July and 6 September, respectively. The intervals between successive rounds in the same village were 61 to 66 days In 1973 spraying was applied in April, June and August and in the southern part in October. The intervals between successive rounds were 56 to 66 days Spray coverage: 74% to 100% (99% on average).
Outcomes	(1) Prevalence rate. (2) Incidence rate. (3) Infant mortality rate
Notes	Study location: Garki District in Northern Nigeria. EIR at baseline in treated villages: wet season:18 to 132; dry season: 0 (except Sugungum: 13) EIR at baseline in untreated villages: wet season:17 to 37; dry season: N/A Malaria endemicity: stable, seasonal. Main vector: *Anopheles gambiae* and *Anopheles funestus.* Material of wall sprayed: clay. Insecticide resistance: None mentioned.

Risk of bias

Molineaux 1980 (*Continued*)

Bias	Authors' judgement	Support for judgement
Blinding? Malaria infections	High risk	
Incomplete outcome data addressed? Malaria infections	Low risk	
Free of selective reporting?	Unclear risk	There is insufficient information to permit a judgement
Free of other bias?	Low risk	

Rowland 2000

Methods	Study design: cluster-randomized controlled trial. Unit of allocation: sectors; the study area comprising 60 villages was divided into nine sectors of approximately equal population size and surface area and then each sector was assigned at random to control, Wettable Powder (WP), or suspension concentrate (SC) formulation Number of units: 3:3:3 sectors. During analysis the two insecticide groups (WP and SC) were merged into a single group because there was no evidence of difference between them Length of follow-up: 2 months before intervention and 7 months after spraying done in June 1997 (one season) Active case detection by home visits every fortnight. Blood slides were taken from any member of a household reporting to having had fever during the previous three days. Monitoring from April 1997 to January 1998, covering the entire malaria transmission season Two cross-sectional surveys were carried out in April-May and September 1997, i.e. before and after the spraying, which was done in June 1997 (one survey within and one survey outside the malaria season, which runs from June to November) To assess the prevalence rate, blood slides were taken from children of one or two schools selected from sentinel villages in each sector Drop-out rates unknown. Confidence intervals were not adjusted for clustering by authors. We could adjust the incidence and prevalence data retrospectively. See Data collection and analysis for more details.The rate ratio (RR) of IRS vs no IRS was estimated by a generalized linear model with negative binomial mean and variance functions. This model sowed to best fit the observed cluster-level incidence rates (Generalized Pearson statistics=1.29)
Participants	(1) Active case detection: Number enrolled:18,000 (2000 in each of the 9 sectors). Inclusion criteria into active surveillance group: any member of a household who reported having had fever during the previous 3 days Exclusion criteria: No explicit exclusion (all ages). (2) Cross-sectional surveys: Inclusion criteria: School children aged 5 to 15 years present in school on the day of the

Rowland 2000 (*Continued*)

	survey Number enrolled: 200 to 300 children per sector. Exclusion criteria: none.
Interventions	Alpha-cypermethrin WP and SC; dosage 25 mg/m²; living quarters, storage rooms and animals shelters were sprayed with Hudson X-pert spray pumps Spray coverage: WP: 96%, SC: 97%.
Outcomes	(1) Malaria incidence through active case detection (P. falciparum and P. vivax) (2) Malaria prevalence through cross-sectional surveys (P. falciparum and P. vivax)
Notes	Study location: 3 Union Councils, covering 180 km² of Sheikhupura District, Punjab Province, approximately 60 km west of Lahore, Pakistan EIR: < 1 Malaria endemicity: not known (annual incidence of 50 episodes per 1000 person years) Malaria season: June to November. Main vector: *Anopheles stephensi.* Material of wall sprayed: mud and brick. Insecticide resistance: no detected resistance, 100% mortality of laboratory-reared and wild-caught *A. stephensi.*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Quote: "..each sector was assigned at random to untreated, WP, or SC spraying..." Comment: Insufficient information for judgement
Allocation concealment?	Unclear risk	Insufficient information for judgement
Blinding? Malaria infections	High risk	
Incomplete outcome data addressed? Malaria infections	Unclear risk	This outcome was not addressed by the study
Free of selective reporting?	Unclear risk	There is insufficient information to permit a judgement
Free of other bias?	Low risk	

Sharp 2007

Methods	Study design: interrupted time series. Only results for zone 1 (enough follow-up time before and after, no spraying interruption) were considered Length of follow-up before intervention: 2 years (1999 to 2000) Length of follow-up after intervention: 5 years (2001 to 2005) Cross-sectional studies were done once per year (in June) within 26 sentinel sites. From a random sample of individuals malaria infections were tested by Rapid Diagnostic Tests (RDTs)
Participants	First year (1999): all age groups included but data also analysed for age group 2 to 14 years. In subsequent years (2000 to 2005) children between 2 to 14 years were included in surveys
Interventions	Bendiocarb; 400 mg/m², twice per year. Spraying was done using Hudson pumps. Spraying personnel were trained in spraying techniques, safety measures and received personal protection equipment
Outcomes	(1) Malaria prevalence of P. falciparum
Notes	Study location: Maputo Province in Southern Mozambique. EIR: > 1 before control activities started. Malaria endemicity: stable malaria before control activities started Main vector:*A. arabiensis; A. funestus.* Material of wall sprayed: Not known. Insecticide resistance: None.

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Malaria infections	High risk	
Incomplete outcome data addressed? Malaria infections	Unclear risk	This was not addressed by the study.
Free of selective reporting?	Unclear risk	There is insufficient information to permit a judgement.
Free of other bias?	High risk	Quote 1: "IRS was interrupted from 2001 to 2002 because of resource constraints, but resumed in the second half of 2003" Comment: Due to the interruption of IRS, it is likely that the effect of the spraying will be underestimated Quote 2: "All age categories were sampled in December 1999, and subsequent surveys were confined to children two to 14 years of age" Comment: In a malaria endemic area, the

Sharp 2007 (*Continued*)

		risk of infection is higher for children than for adults. Therefore the prevalence might be affected when comparing the year with all age groups compared to the years with children only. However, looking at the difference in the prevalence rates of the year with all age-groups surveyed versus subsequent years, this effect seems negligible

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Afifi 1959	Data collection for groups not contemporaneous.
Afridi 1947	Not enough units/arm.
Alves 1953	Usage of an insecticide (Benzene Hexachloride (BHC)) which is not recommended by WHO
Andrews 1951	Review, not enough data to analyse.
Ansari 1986	Inappropriate choice of control site (Hexachlorocyclohexane (HCH) spraying)
Ansari 1990	Inappropriate choice of control site (HCH spraying).
Ansari 2004a	Inappropriate choice of control site (Malathion spraying); not enough units/arm
Ansari 2004b	Inappropriate choice of control site (HCH spraying).
Arredondo-Jimenez 1993a	Inappropriate choice of control site (DDT spraying).
Arredondo-Jimenez 1993b	Not enough units/arm.
Barai 1982	Review, not enough data to analyse.
Barutwanayo 1991	ITS with mix of interventions (IRS, ITN, drainage and improvement of health system)
Bhatnagar 1974	Dosage of insecticide application not concurrent with WHO recommendations
Bradley 1991	Usage of an insecticide (Benzene Hexachloride (BHC)) which is not recommended by WHO
Brieger 1996	Not enough data to analyse (denominators missing); author was contacted but could not supply missing data
Cai 1999	Not enough units/arm.

(*Continued*)

Cavalié 1961a	not enough data for pre- and post-intervention assessment.
Cavalié 1961b	not enough data for pre- and post-intervention assessment.
Charlwood 1995	Inappropriate choice of control site (lambdacyhalothrin spraying); not enough units/arm; not enough data for pre-intervention assessment
Conteh 2004	Non-eligible outcomes measured.
Coosemans 1978	Review, not enough data to analyse.
Coosemans 1989	Not enough data for quality assessment and analyses of the data
Coosemans 1991	ITS with mix of interventions (IRS, ITN, drainage and improvement of health system)
Coppen 1999	Not enough data, conference abstract only; author could not be contacted for additional information
Cot 1999	Not enough data, conference abstract only; author could not be contacted for additional information
Cot 2001	not enough units/arm.
Cot 2002	Non-eligible outcomes measured.
Curtis 1999	Not enough data, conference abstract only.
Curtis 2000	Review, not enough data to analyse.
Dapeng 1996	Interrupted times series with mixed malaria control interventions (IRS and ITN)
Das 1987	Inappropriate choice of control site (DDT spraying).
de Zulueta 1954	Not enough units/arm; collection of data in control and survey area at different time points
de Zulueta 1961	Not enough data for pre-intervention assessment; ITS with mixed interventions (IRS and treatment)
Deane 1948	Not enough data for pre/post-intervention assessment.
Dhiman 2005	ITS with mixed interventions (IRS and treatment).
Dodge 1965	Not enough data for pre-intervention assessment.
Doke 2000	Not enough data for pre/post-intervention assessment.
Dowling 1950	Inappropriate choice of control site.
Dowling 1951	Inappropriate choice of control site.

(*Continued*)

Eddey 1944	Not enough data for post-intervention assessment.
Edeson 1957	Not enough units/arm.
Farid 1954	ITS with mixed interventions (IRS and larviciding); mix of refugee and general population
Faye 1992	Not enough units/arm; wrong dosage of insecticide (1g/m2 fenitrothion)
Fontaine 1976	Not enough units/arm.
Fontaine 1978	Not enough units/arm.
Gandahusada 1984	Non randomised allocation of intervention.
Gill 1997	Not enough units/arm.
Gunasekaran 2005	IRS coverage below 60%.
Guyatt 2002	Inappropriate choice of control site.
Hamon 1954	ITS with mixed interventions (IRS, larviciding and drug distribution)
Hii 1993	Study sites not comparable.
Ismail 1974	Not enough data for post-intervention assessment.
Ismail 1975	High level of population movement.
Ismail 1978	Not enough data for pre- and post-intervention assessment.
Jaggi 1984	Not enough data for pre-intervention assessment.
Jambou 2001	Control group not comparable; not enough data for pre-intervention assessment
Kamolratanakul 2001	Not enough data for quality assessment.
Kleinschmidt 2006	Not enough data for pre- and post-intervention assessment.
Kleinschmidt 2007	Not enough data for pre-intervention assessment.
Lambrecht 1952	Not enough data for pre-intervention assessment.
Lantoarilala 1998	Not enough units/arm.
Maharaj 2005	Not enough data for post-intervention assessment.

(*Continued*)

Mastbaum 1951	Not enough units/arm.
Matola 1981	Usage of an insecticide (Dieldrin) which is not recommended by WHO
Metselaar 1954	Not enough units/arm.
Metselaar 1957	Not enough units/arm.
Metselaar 1960	Not enough data for pre-intervention assessment.
Metselaar 1961	ITS with mixed interventions (IRS and drug distribution).
Mnzava 1993	Not enough units/arm.
Najera 1965	Not enough units/arm; Inappropriate choice of control site.
Najera 1967	Not enough units/arm.
Najjar 1959	Not enough data for pre-intervention assessment.
Nalim 1997	Not enough units/arm.
Nasir 1982	Not enough data on parasitological assessment.
Nguyen 1996	Not enough units/arm.
Nyarango 2006	Application of mixed interventions (IRS, ITN, larviciding and malaria case management)
Onori 1975	Not enough units/arm; not enough data for pre and post-intervention assessment
Over 2003	Non-expermimental approach to analyse the impact of malaria intervention
Over 2004	Non-expermimental approach to analyse the impact of malaria intervention
Pampana 1950	Review, not enough data to analyse.
Pardo 2006	Not enough data for pre-and post-intervention assessment.
Pattanayak 1980	Not enough units/arm.
Payne 1976	Non enough units/arm.
Pletsch 1954	Not enough units/arm.
Protopopoff 2008	Control site not comparable.

(*Continued*)

Pujara 1983	Inappropriate choice of control site and not enough units/arm
Rachou 1966	Not enough units/arm.
Rafi 1954	Not enough data for pre-intervention assessment.
Rajendram 1951	Insecticide (BHC) not recommended by WHO.
Rajendram 1951a	Insecticide (BHC) not recommended by WHO.
Rakotomanana 2001	Non-eligible outcomes measured.
Reisen 1993	Not enough units/arm.
Rodriguez 1994	Non-eligible outcomes measured.
Rodríguez 1993	Mix of intervention (IRS and drug distribution).
Romi 2002	Not enough data for pre- and post- intervention assessment.
Rowland 1994	Before-after comparison, no control group. Actual randomized comparison is between early and late spraying
Rowland 1997	13 intervention clusters but only one control cluster (instead of 3 required). Malathion results low, presumably as result of resistance in local vectors
Russel 1939	Not enough units/arm.
Russel 1942	Not enough units/arm.
Sahondra 2001	ITS with mixed interventions (IRS and drug distribution).
Sahu 1993	Not enough units/arm (only 1 control village).
Sahu 1995	Non-eligible outcomes measured.
Saliternik 1977	Review, not enough data to analyse.
Sastry 1961	Review, not enough data to analyse.
Sexton 1994	Not enough data, conference abstract only.
Sharma 1982	DDT spraying in area with DDT resistant *A. culicifacies.*
Sharma 1985	Not enough units/arm.

(*Continued*)

Sharma 1986	Inappropriate choice of control site.
Sharma 1996	Not enough units/arm; spray coverage too low for malathion spraying
Sharma 2005	Inappropriate choice of control site (DDT-spraying).
Sharp 2002	Not enough data for post-intervention assessment.
Singh 2006	ITS with mixed interventions (IRS, early detection and treatment, larvivorous fishes)
Taylor 1986	Not enough units/arm.
Tewari 1990	ITS with mixed interventions (IRS, space-spraying and anti-larval measures)
Trapido 1946	Not enough units/arm.
van Thiel 1951	Not enough units/arm.
van Wyk 2002	Not enough data, conference abstract only.
Verdrager 1975	Not enough units/arm.
Viswanathan 1947	Inappropriate choice of control site.
Viswanathan 1950	Mix of dosages used for IRS (two of them not in line with WHO recommendations)
Wattal 1978	Dosage of insecticide application not in line with WHO recommendations
WHO 2007	ITS with mixed interventions (IRS and anti-larval measures).
Wilson 1954	Not enough units/arm.
Wu 1984	Not enough units/arm.
Wu 1993	Inappropriate choice of control site.
Xu 1998	Not enough units/arm.
Xu 2002	Inappropriate choice of control site.
Zaphiropoulos 1959	Not enough data for pre-intervention assessment.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kere 1992

Methods	RCT
Participants	Unknown because thesis not available
Interventions	Unknown because thesis not available
Outcomes	Unknown because thesis not available
Notes	

ADDITIONAL TABLES

Table 1. Detailed search strategies

Search set	CIDG SR[a]/LILACS[b]	CENTRAL/MEDLINE[b]	EMBASE[b]	LILACS[b]
1	malaria	malaria	malaria	malaria
2	insecticide*	insecticide*	insecticide*	insecticide*
3	indoor residual spray*	indoor residual spray*	indoor residual spray*	indoor residual spray*
4	IRS	house spray*	IRS	IRS
5	house spray*	IRS	house ADJ spray$	house spray*
6	2 or 3 or 4 or 5	MOSQUITO CONTROL/ INSTUMENTATION/ METHODS	VECTOR CONTROL	2 or 3 or 4 or 5
7	1 and 6	INSECTICIDES/ THERAPEUTIC USE	INSECTICIDE	1 and 6
8		PYRETHRINS/ADMINIS-TRATION AND DOSAGE	2-7/OR	
9		2-8/OR	1 and 8	
10		1 and 9		

[a]Cochrane Infectious Diseases Group Specialized Register [b]Upper case: MeSH or EMTREE heading; Lower case: free text term

Table 2. Trial characteristics of major factors influencing the impact of IRS

Trial	EIR[a]	Insecticide	Insecticide resistance	Main vector	Dominant wall type	Co-intervention(s)	Pre-trial control measures
Pakistan (Rowland 2000)	< 1	Alphacypermethrin	No	*A. stephensi*	Mud/brick	Treatment of fevers	IRS (for 25 years)
India (Misra 1999)	< 1	Deltamethrin	yes[b]	*A.culicifacies*	Mud/brick	IEC[d]	IRS (for 60 years)
South Africa (Mnzava 2001)	< 1	Deltamethrin	No[c]	*A.arabiensis*	N/A	IEC[d]	IRS (for 50 years)
Tanzania (Curtis 1998)	> 1	Lambdacyhalothrin	No	*A.gambiae* *A.funestus* *A.arabiensis*	Mud	None	Clearing of malaria infections
Nigeria (Molineaux 1980)	> 1	Propoxur	No	*A.gambiae* *A.arabiensis* *A.funestus*	Clay	None	None
Mozambique (Sharp 2007)	> 1	Bendiocarb	No	*A.arabiensis* *A.funestus*	N/A	Treatment of slide - positive participants	None

[a] Transmission intensity (EIR: Entomological inoculation rate - indicates how many infectious mosquito bites a person receives on average per year)
[b] Mortality range for WHO susceptibility test: 74.4% to 96.5%
[c] Within other areas in Kwa-Zulu Natal, *A. funestus* was shown to be resistant to deltamethrin. However, there was no evidence that pyrethroid-resistant *A. funestus* were present in the area during the reported study
[d] IEC: Information, Education and Communication

Table 3. Outcomes of studies

		Comparisons		Outcomes				
Study	**Study design**	**IRS vs no IRS**	**IRS vs ITN**	**Incidence of re-infection**	**Incidence of infection**	**Infant parasite conversion rate**	**Prevalence of infection**	**Anaemia**
Tanzania (Curtis 1998)	RCT	X	X	X	X		X	X

Table 3. Outcomes of studies (*Continued*)

South Africa (Mnzava 2001)	RCT		X		X			
Pakistan (Rowland 2000)	RCT	X			X		X	
India (Misra 1999)	RCT	X	X		X		X	
Nigeria (Molineaux 1980)	CBA	X				X	X	
Mozambique (Sharp 2007)	ITS	X					X	

Table 4. IRS versus no IRS (stable malaria areas); incidence and prevalence; RCT

Outcome measure	Age groups	Study	IRS	Control	Rate/Risk ratio (RR)	95% confidence interval	Protective efficacy of IRS
Incidence of reinfection	Children 1 to 5 years	Curtis 1998 (Tanzania)	468/3840[a]	1014/3840[a]	0.46	0.42 to 0.51[b]	54%
Parasite incidence[c]	Children 1 to 5 years	Curtis 1998 (Tanzania)	228/413	304/471	0.86	0.77 to 0.95[b]	14%
	Children older than 5 years	Curtis 1998 (Tanzania)	381/1007	365/984	1.02	0.91 to 1.15[b]	-2%
Parasite prevalence[d]	Children 1 to 5 years	Curtis 1998 (Tanzania)	135/212	162/240	0.94	0.82 to 1.08[b]	6%

[a] Denominator are person-weeks, hence RR is a rate ratio
[b] Not adjusted for clustering
[c] Incidence rates calculated for the whole year 1996
[d] Calculated on last cross-sectional survey (4th quarter 1996)

Table 5. IRS versus no IRS (stable malaria areas): infant parasitological conversion rates[a] of *P.falciparum*; CBA

Study	Treatment	year		
		1971[b]	**1972[c]**	**1973[c]**
Molineaux 1980 (Nigeria)	IRS	0.012	0.002	0.002
	no IRS	0.016	0.005	0.009

[a] Infant parasitological conversion rate: -ln(1-p)/t, where p= conversion rate and t= time
[b] Before intervention
[c] After intervention

Table 6. IRS versus no IRS (stable malaria areas): crude parasite prevalence rates (seasonal average); CBA

Comparison	Study	IRS	no IRS	Risk ratio	95% Confidence interval	Protective efficacy
STABLE MALARIA IRS vs no IRS: dry season: any infection	Molineaux 1980 (Nigeria)	700/2310	405/1261	0.94	0.85 to 1.04	6%
STABLE MALARIA IRS vs no IRS: wet season: any infection	Molineaux 1980 (Nigeria)	809/2310	599/1261	0.74	0.68 to 0.80	26%

Table 7. IRS versus no IRS (stable malaria areas): prevalence of *P. falciparum;* ITS

Study	Year	1999	2000[a]	2001	2002	2003	2004	2005
Sharp 2007 (Mozambique)	**% (n)**	65 (597)	60 (918)	38 (807)	22 (824)	8 (792)	7 (839)	4 (698)
	95% CI[b]	45-80	36-81	25-53	11-39	5-13	5-11	3-6

[a] Start of spraying in November 2000
[b] Adjusted for clustering

Table 8. IRS versus no IRS or IRS versus ITNs (stable malaria areas); impact on haemoglobin levels; RCT

Comparison	Study	Haemoglobin (in g/dL) n = number of participants IRS group	Haemoglobin (in g/dL) n = number of participants Control group	MD[a]
IRS vs no IRS	Curtis 1998 (Tanzania)	10.24 n = 212	9.39 n = 240	0.85
IRS vs ITN	Curtis 1998 (Tanzania)	10.24 n = 212	10.18[b] n = 237	0.06

[a] MD: Mean Difference, one year after start of implementation (4th quarter 1996).
[b] ITN group

Table 9. IRS versus no IRS (unstable malaria areas); incidence and prevalence; RCT

Outcome measure	Infection	Age groups	Study	IRS	No IRS	Risk ratio	95% confidence interval	Protective efficacy of IRS
Parasite incidence	Any infection	All ages	Misra 1999 (India)	1497/44042	2195/44351	0.69	0.64-0.73[b]	31%
			Rowland 2000 (Pakistan)	69/11694	317/6567	0.12	0.04 to 0.31[a]	88%
	P. falciparum	All ages	Rowland 2000 (Pakistan)	23/11694	194/6567	0.07	0.02 to 0.39[a]	93%
	P. vivax	All ages	Rowland 2000 (Pakistan)	46/11694	123/6567	0.21	0.10 to 0.55[a]	79%
Parasite prevalence	Any infection	All ages	Misra 1999 (India)	84/26085	119/26589	0.72	0.54 to 0.95[b]	28%
		Children 5 to 15 years	Rowland 2000 (Pakistan)	41/1528	94/831	0.24	0.17-0.34[b]	76%
	P. falciparum	All ages	Misra 1999 (India)	64/26085	99/26589	0.66	0.48 to 0.90[b]	34%
		Children 5 to 15 years	Rowland 2000 (Pakistan)	5/1528	32/831	0.08	0.03 to 0.22[b]	92%

Table 9. IRS versus no IRS (unstable malaria areas); incidence and prevalence; RCT (*Continued*)

	P.vivax	All ages	Misra 1999 (India)	20/26085	20/26589	1.02	0.55 to 1.89[b]	-2%
		Children 5 to 15 years	Rowland 2000 (Pakistan)	36/1528	62/831	0.32	0.21 to 0.47[b]	68%

[a] Adjusted for clustering
[b] Not adjusted for clustering
[c] ICC=Intracluster correlation

Table 10. IRS versus ITNs (stable malaria areas); incidence and prevalence; RCT

Outcome measure	Age groups	Study	IRS	ITN	Risk ratio	95% confidence interval	Protective efficacy of IRS
Incidence of reinfection	Children 1 to 5 years	Curtis 1998 (Tanzania)	468/3840[a]	384/3840[a]	1.22	1.07 to 1.38[b]	-22%
Parasite incidence[c]	Children 1 to 5 years	Curtis 1998 (Tanzania)	228/413	255/405	0.88	0.78 to 0.98[b]	12%
	Older than 5 years	Curtis 1998 (Tanzania)	382/1007	346/893	0.98	0.87 to 1.10[b]	2%
Parasite prevalence[d]	Children 1 to 5 years	Curtis 1998 (Tanzania)	135/212	143/237	1.06	0.91 to 1.22[b]	-6%

[a] Denominator are person-weeks
[b] Not adjusted for clustering
[c] Incidence rates calculated for the whole year 1996
[d] Calculated on last cross-sectional survey (4th quarter 1996)

Table 11. IRS versus ITNs (unstable malaria areas); incidence and prevalence; RCTs

Outcome measure	Infection	Age groups	Study	IRS	ITN	Risk ratio	95% confidence interval	Protective efficacy of IRS
Parasite incidence	Any infection	All ages	Misra 1999 (India)	1497/44042	1014/44158	1.48	1.37 to 1.60[a]	-48%
	Any infection	All ages	Mnzava 2001 (South Africa)	1814/7649	966/5450	1.34	0.77 to 2.70[b]	-34%

Table 11. IRS versus ITNs (unstable malaria areas); incidence and prevalence; RCTs (*Continued*)

Parasite prevalence	Any infection	All ages	Misra 1999 (India)	84/26085	51/26849	1.70	1.18 to 2.44[a]	-70%
	P. falciparum	All ages	Misra 1999 (India)	64/26085	37/25904	1.78	1.19-2.67[a]	-78%
	P. vivax	All ages	Misra 1999 (India)	20/26085	20/26849	1.37	0.70 to 2.68[a]	-37%

[a] Not adjusted for clustering
[b] Adjusted for matching, but not for clustering

WHAT'S NEW

Date	Event	Description
13 April 2010	Amended	Plain language summary added

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 4, 2010

Date	Event	Description
29 April 2008	Amended	Converted to new review format.
17 May 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

BP: reference identification, screening, retrieval of papers for eligibility, data extraction, analysis of data, main writing. FT: preliminary reference identification, screening retrieved papers for eligibility, contribution to writing. CL: initial concept, organization of reference searching, second data extraction, contribution to writing and supervision. BS: Initial concept, technical inputs in technical matters. Sadly, BS passed away during the initial phase of the review. His experience, drive and good nature are sorely missed.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Durban, South Africa.
- Medical Research Council, Durban, South Africa.
- Swiss Tropical Institute, Basel, Switzerland.
- Rudolf Geigy Foundation, Basel, Switzerland.

External sources

- United States Agency for International Development (USAID), Washington D.C. through Research Triangle Institute (RTI), USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We planned to convert the outcomes for anaemia presented as g/dL into packed cell volume with a standard factor of 1:3. But Carneiro 2007 showed that this conversion is not always accurate and since we only had one trial providing haemoglobin measures, we presented them as they were presented within the paper (in g/dL).

We did not find individually randomized RCTs in the frame of this review. However, the methods of extracting data and analysing such trials would follow the methods outlined in the protocol.

We did not do a sensitivity analysis due to the small number of trials. However, the methods published in the protocol will be followed, if appropriate, in future updates of this review.

We only found one eligible ITS for our review and presented its results as shown in the paper. If further trials will be included in future updates we will analyse them as published in the protocol.

Methological quality was assessed using the Cochrane Collaboration's risk of bias tool (Higgins 2008).

No summary of the major debates and findings of other reviews on DDT was included in the discussion as none of our included studies used DDT as insecticide.

There was a change in the authorship. BP replaced FT as first author because she took the lead in this work.

INDEX TERMS

Medical Subject Headings (MeSH)

*Insect Vectors; *Insecticide-Treated Bednets; *Insecticides; Africa South of the Sahara [epidemiology]; Incidence; India [epidemiology]; Malaria [epidemiology; *prevention & control]; Mosquito Control [*methods]; Pakistan [epidemiology]; Pesticide Residues; Randomized Controlled Trials as Topic

MeSH check words

Animals; Humans