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[Intervention Review]

Insecticide space spraying for preventing malaria transmission

Joseph Pryce¹, Leslie Choi¹, Marty Richardson², David Malone³

¹Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK. ²Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, UK. ³IVCC, Liverpool School of Tropical Medicine, Liverpool, UK

Contact address: Joseph Pryce, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK. joseph.pryce@lstmed.ac.uk.

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ABSTRACT

Background

Space spraying is the dispersal of a liquid fog of insecticide into an outdoor area to kill adult insects. It has been regularly used in public health and pest control programmes, including use as an emergency response to malaria epidemics. This Cochrane Review aims to assist the decision-making of malaria vector control programmes by summarizing the evidence of the impact of space spraying on malaria transmission.

Objectives

The review's primary objective was to evaluate the impact of space spraying on malaria transmission, or the incremental impact when applied in combination with other malaria control methods, in comparison to equivalent conditions with no space spraying intervention.

To guide future evaluations of space spraying, a secondary objective was to identify and summarize the range of space spraying strategies that have been trialled, those which were promising and warrant further evaluation, and those which appear unlikely to warrant further evaluation (for example, if they were not feasible to implement, or were unacceptable to the population).

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; PubMed (MEDLINE); Embase (OVID), CAB Abstracts (Web of Science), LILACS (BIREME), the World Health Organization (WHO) International Clinical Trials Registry Platform, and ClinicalTrials.gov up to 18 April 2018. We contacted organizations for ongoing and unpublished trials, and checked the reference lists of all included studies for relevant studies.

Selection criteria

We included cluster-randomized controlled trials, interrupted time series (ITS) studies, randomized cross-over studies, and controlled before-and-after (CBA) studies comparing space spraying with no space spraying that met the inclusion criteria for the review.

Data collection and analysis

Two review authors independently assessed trials for eligibility and risk of bias, and extracted the data. For ITS studies, we present findings graphically, and estimated the effect of space spraying on the step change and the slope change. We assessed the certainty of evidence using the GRADE approach.

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Main results

Two ITS studies, conducted between 1972 and 1984, met our inclusion criteria for the primary objective, and one study contributed to the quantitative analysis. This study was conducted in India, reported the incidence of malaria in four separate sites, and covered a total population of 18,460 people. In the pooled analysis across sites, there was no step effect for the incidence of uncomplicated malaria (step rate ratio 1.00, 95% confidence interval (CI) 0.51 to 1.92). There was an effect on the slope: the number of cases was reduced by 15% per month (slope rate ratio 0.85, 95% CI 0.79 to 0.91). Using these ratios, we estimated the effect of 12 months of space spraying on malaria incidence to be a reduction from 6 cases to 1 case per month per 1000 population (95% CI 0 to 2 cases, very low-certainty evidence). The second study reported the impact of space spraying on malaria incidence and adult mosquito density in a population of 15,106 in Haiti, but it did not provide data from previous years. Thus, we could not estimate an effect of space spraying that was independent from temporal trends.

For the review's secondary objective, we identified a further two studies in addition to the two ITS studies; both used a CBA design and were conducted between 1973 and 2000. The four studies used a range of delivery methods including handheld, vehicle-mounted, and aircraft-mounted spraying equipment. A variety of insecticides, doses, and spraying times were also used, with methods typically determined based on environmental factors and vector profiles.

Authors' conclusions

Evidence from one state in India conducted over 30 years ago suggests an effect of space spraying on the incidence of malaria, but the certainty of the evidence is very low. Reliable research in a variety of settings will help establish whether and when this intervention may be worthwhile.

PLAIN LANGUAGE SUMMARY

Insecticide space spraying for preventing malaria transmission

What is space spraying and how might it work?

Space spraying is the outdoor spraying of insecticides to kill adult insects. The insecticide is dispersed using hand-held, vehicle-mounted or aircraft-mounted equipment to produce a fog. Space spraying is regularly used in public health and pest control programmes, including use as an emergency response to malaria epidemics. Insecticide-treated bed nets and indoor spraying of insecticides are the two interventions most commonly used by malaria programmes to control mosquito populations. Both interventions are effective at reducing human contact with indoor-biting mosquito species. If successful, space spraying reduces populations of outdoor-biting mosquitoes, and may help reduce malaria transmission from the mosquito species least affected by typical control efforts. At present, however, there remains widespread uncertainty over whether space spraying has any impact on malaria transmission.

What is the aim of the review?

In order to guide decision-making for malaria control programmes, the aim of this Cochrane Review was to summarize the actions taken and reported findings of trials evaluating the impact of space spraying on malaria transmission.

What are the main findings of the review?

After searching for relevant trials up to 18 April 2018, we identified four studies conducted between 1972 and 2000. Across the four studies, a range of insecticide delivery methods were used, including handheld, vehicle-mounted, and aircraft-mounted spraying equipment. A variety of different insecticides, doses, and spraying times were also used to suit the local environment and the behaviour of the targeted mosquito species.

In three studies, the evidence was considered to be unsuitable for reliably assessing the impact of space spraying on the number of cases of malaria. The remaining study, which took place in a single state in India and covered a combined population of 18,460 people, reported the number of malaria cases in the years preceding and following the introduction of space spraying. The evidence suggested that space spraying led to a decrease in the number of cases of malaria, but as the trial was conducted over 30 years ago and within one state in India, we cannot be certain that these findings are applicable in other areas where malaria occurs. Reliable research in a variety of settings will help to establish whether and when this intervention may be worthwhile.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Space spraying compared to no space spraying for reducing malaria transmission						
Patient or population: people of all ages Setting: malaria transmission areas Intervention: space spraying Comparison: no space spraying						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no space spraying ^a	Risk following space spraying ^b				
Malaria cases per month	6 per 1000	Instant effect: 6 per 1000 (3 to 12) Effect after 12 months follow-up: 1 per 1000 (0 to 2 per 1000)	Step rate ratio: 1.00 (0.51 to 1.92) Slope rate ratio: 0.85 (0.79 to 0.91)	(1 observational study: 4 sites)	⊕○○○ VERY LOW ^{c,d,e} downgraded due to risk of bias, indirectness, and imprecision	We do not know if space spraying causes an immediate shift in the trend of malaria incidence over time or a change in the slope of the trend (that is, a proportional reduction in cases per month)

* **The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aWe estimated the risk with no space spraying by calculating the mean monthly incidence of malaria across each of the study sites. We include only incidence data from complete years (January to December without intervention) in the calculation.

^bWe estimated the instant effect following the introduction of space spraying by multiplying the risk with no space spraying by the step rate ratio (i.e. the 'immediate' shift in the incidence trend). We used the CI for the step rate ratio to calculate the CI for the instant effect. We estimated the effect after 12 months follow-up by multiplying the risk with no space spraying by the slope rate ratio (the reduction in cases of malaria per additional month of follow-up) for each of the 12 months. We used the CI for the slope rate ratio to calculate the CI for the risk following 12 months of the intervention.

^cDowngraded by one for serious risk of bias: [Tewari 1990](#) shows evidence of selective reporting of incidence, with data presented from just four of the 24 villages in Vanapuram indicated to have received the intervention.

^dDowngraded by one for serious indirectness: only one study is included in the analysis, conducted in Tamil Nadu, India. It is unclear if the effect reported here would be similar in other malaria transmission areas with different ecological landscapes, climates and primary vector species.

^eDowngraded by one for serious imprecision: the CI of the step rate ratio is large and includes both a sizeable increase and a reduction in malaria incidence.

BACKGROUND

Description of the condition

With one child dying from malaria every two minutes, malaria remains the world's most serious vector-borne disease. In 2016, an estimated 216 million new cases arose globally and the disease caused 445,000 deaths, of which more than two-thirds were children under the age of five (WHO 2017a). Most of the malaria burden falls on people living in sub-Saharan Africa, where 90% of the total incidence and 91% of all deaths occur (WHO 2017a). Malaria is also a leading cause of global morbidity and was responsible for between 63 and 110 million disability-adjusted life years (DALYs) in 2010 (Murray 2012).

The *Plasmodium* species that cause malaria are transmitted by the bite of a female *Anopheles* mosquito, and malaria prevention methods are predominantly geared towards reducing human contact with infective mosquitoes. Insecticide-treated nets (ITNs) and indoor residual spraying (IRS) prevent malaria transmission in a variety of settings, and these methods have formed a central component of the global strategy for malaria control (Lengeler 2004; Pluess 2010; WHO 2015). Between 2010 and 2015 the estimated percentage of the at-risk population sleeping under an ITN rose from 30% to 53%. This drive has coincided with a reduction in disease incidence of 21%, while malaria-related deaths have fallen by 29% (WHO 2016a). However, these successes have not been

universal. Of the 91 countries with active transmission of malaria, only 40 are on course to achieve the Global Technical Strategy's target of a 40% incidence reduction by 2020 (WHO 2015; WHO 2016a).

Description of the intervention

Space spraying refers to the process of dispersing liquid droplets of insecticide into an area as a fog, with the aim of knocking down and killing adult insects (Figure 1). For the purposes of this Cochrane Review, the term implies distribution of insecticide at a population level, rather than household use. There are two different mechanisms for generating the fog for space spraying. Thermal fogs use hot gas to vaporize a solution of insecticide in a typically oil-based carrier liquid. Upon spraying, the vapour interacts with colder air and forms a dense fog. In contrast, cold fogs are formed without the use of external heat, passing the insecticide mixture instead through a mechanical apparatus such as a high-pressure nozzle or high-speed air flow. Cold fogging commonly uses ultra-low-volume (ULV) preparations of insecticide. The insecticide may also be delivered in three different ways; using equipment that is either hand-held, vehicle-mounted, or applied from an aircraft (WHO 2003). Table 1 details the insecticides and doses currently recommended by the World Health Organization (WHO) for space spraying use to control mosquitoes (WHO 2016b).

Figure 1. Space spraying with hand-held equipment to control the mosquito population in Thailand



Space spraying is regularly used in other public health and pest control programmes. The intervention is an often-used strategy in response to outbreaks of dengue fever, a mosquito-borne viral disease with endemic regions that overlap extensively with those of malaria (Epelboin 2012). However, there is a lack of robust evidence that the strategy impacts on dengue transmission (Esu 2010). Both ground and aerial spraying of insecticides have also been regularly used for the control of tsetse flies and for other pests of public health or agricultural importance (WHO 2003; Adam 2013).

Both thermal and cold fog applications are only effective while the droplets remain airborne (WHO 2003). The length of this time is mainly dependent on the size of droplets distributed; a 10 μm droplet spray will fall by 10 metres in one hour, while 100 μm droplets will fall the same distance in 36 seconds. *Anopheles* mosquitoes typically bite in the evening, at night and in the early morning, and it is recommended that the timing of spraying coincides with this period of peak activity (WHO 2003; Pates 2005). Space spraying is sometimes conducted during the day. In these cases, the intention is to reach and kill mosquitoes in their resting locations, or induce them to take flight through the fog (Najera 2003). Space spraying targets only the current adult mosquito population. The technique has little or no residual activity, and as juvenile stages are not vulnerable to space spraying, multiple applications are required to prevent the adult population being replaced (Najera 2003; Bonds 2012).

How the intervention might work

George Macdonald's theory of vectorial capacity can be used to explain the impact of malaria vector control interventions. Vectorial capacity is a theoretical estimate of the intensity of transmission, equivalent to the basic reproduction ratio of a disease. It describes the total number of potentially infectious bites that would eventually arise from all the mosquitoes in a population biting a single perfectly-infectious human on a single day. The Ross-Macdonald model shows that vectorial capacity is highly sensitive to interventions that target the adult mosquito population, as they cause a reduction in both the ratio of mosquitoes to humans and the probability of mosquito survival (Macdonald 1952; Smith 2012). If effective, space spraying interventions will therefore have a direct impact on the intensity of transmission. Assuming that the number of infections arising in humans is relative to the number of infectious bites received, this will further lead to a reduction in the number of clinical cases of malaria (Smith 2007).

Why it is important to do this review

The 2017 World Malaria Report shows the declining trend in malaria cases and deaths since the turn of the millennium has

begun stalling in recent years, and there is a growing need for additional control methods (WHO 2017a). ITNs and IRS successfully exploit the anthropophilic (human-biting), endophilic (indoor resting), endophagic (indoor biting), and nocturnal behaviours of Africa's most efficient malaria vectors: *Anopheles gambiae* and *Anopheles funestus* (Pates 2005; Sinka 2010). In areas of low to moderate transmission, these interventions can be sufficient to reduce parasite prevalence to elimination thresholds, but additional control measures will be required in settings with high transmission or more challenging vector species (Griffin 2010; Chaccour 2016). Space spraying may have a role in reducing transmission in such settings, as it will impact upon those species that are outdoor-biting and therefore more behaviourally resistant to ITNs and IRS. This is of particular interest in the current and future climate, as coverage of ITNs increases and transmission via exophagic and zoophagic vector species becomes more important. The WHO guidelines for judicious insecticide use state that space spraying may be advisable as an emergency response to malaria epidemics, provided that resources are available for its immediate application, and that the approach has previously had success against the target species (Najera 2003). This is particularly recommended for densely-populated areas with little potential for IRS, such as camps for refugees and displaced people (WHO 2013; WHO 2015).

However, the use of space spraying for malaria control has been limited. This may be due to the difficulty associated with undertaking space spraying at night, when *Anopheles* mosquitoes are most active, or the view that day-time fogs do not penetrate into the resting sites of *Anopheles* mosquitoes (Najera 2003). Space spraying may contribute to overall vector control activities in parts of Latin America and Asia, which include targeting against malaria vectors, but due to a shortage of robust evidence there remains widespread uncertainty over whether space spraying has any impact on malaria transmission. Despite its use in a variety of epidemic and emergency situations, there is a perception that space spraying is only performed as a public relations exercise (Najera 2003). Space spraying also carries an expense as it requires both specialized equipment and trained staff, in addition to large quantities of insecticide if implemented on a routine basis.

To achieve a target as ambitious as the eradication of malaria, complete clarity is required about the effectiveness of available control methods. Understanding the impact of space spraying will allow the malaria community, including investors, researchers, and disease-control strategists, to make informed decisions about the allocation of resources and to maximize the benefit of investments.

OBJECTIVES

The review's primary objective was to evaluate the impact of space spraying on malaria transmission, or the incremental impact when applied in combination with other malaria control methods, in comparison to equivalent conditions with no space spraying intervention.

To guide future evaluations of space spraying, a secondary objective was to identify and summarize the range of space spraying strategies that have been trialled, those which were promising and warrant further evaluation, and those which appear unlikely to warrant further evaluation (for example, if they were not feasible to implement, or were unacceptable to the population).

METHODS

Criteria for considering studies for this review

Types of studies

For our primary objective, we included the following types of studies.

- Randomized controlled trials (RCTs). As the intervention is distributed at a community level, we did not expect to find trials with individual randomization. We included cluster-randomized controlled trials (cRCTs) with:
 - the unit of randomization being a cluster;
 - evidence of baseline equivalence;
 - monitoring of at least one transmission season; and
 - at least two clusters per arm.
- Interrupted time series (ITS) designs with:
 - a clearly-defined point in time when the intervention occurred; and
 - at least three data points before and three after the intervention.
- Randomized cross-over studies with:
 - a clearly-defined point in time when the cross-over occurred; and
 - monitoring of at least two transmission seasons before and after the cross-over.
- Controlled before-and-after (CBA) studies with:
 - a contemporaneous control group;
 - monitoring of at least one transmission season before and after the intervention; and
 - at least two sites per treatment arm.

As part of our secondary objective to review a broader range of space-spraying strategies that have been tested, we have also included the following study designs that were considered to provide little or no reliable evidence regarding effects.

- CBA studies with only one site per treatment arm.

- ITS studies with monitoring of at least two time points before and after the intervention.

Types of participants

Children and adults living in malaria transmission settings.

Types of interventions

Intervention

- Interventions that use space spraying of insecticides with the purpose of knocking down and killing adult *Anopheles* mosquitoes.
- Interventions may include thermal fogging or cold aerosols distributed through pedestrian (hand-held/backpack), ground vehicle, or aerial means.
- Insecticides applied in repetitions, with a minimum of two sprays.

Control

- Equivalent regions that did not receive the above-named space-spraying interventions.
- Equivalent regions that received space spraying with an alternative public health insecticide.
- The control group must not have received any other malaria co-intervention(s) that differed from the intervention arm.

Types of outcome measures

We included studies that reported any of the following outcomes.

Primary outcomes

- Incidence: measured as a count per person unit time of (a) infections or (b) new infections, following radical cure to avoid measuring pre-existing infections. We defined infection as any symptom, including fever, with confirmed parasitaemia (by blood smear microscopy or rapid diagnostic test (RDT)).
- Parasite prevalence: the proportion of surveyed individuals with confirmed parasitaemia.

Secondary outcomes

Epidemiological outcomes

- All-cause mortality.
- Number of people with severe disease: we used site-specific definitions, provided they included (a) and either (b) or (c): (a) demonstration of parasitaemia by blood smear; (b) symptoms of

cerebral malaria including coma, prostration, or multiple seizures; (c) severe, life-threatening anaemia.

- Number of people with uncomplicated clinical malaria episodes: we used site-specific definitions, provided they included (a) demonstration of malaria parasites by either blood smear or RDT, or both; and (b) clinical symptoms including fever detected passively or actively.

Entomological outcomes

- Entomological Inoculation Rate (EIR): the estimated number of bites by infectious mosquitoes per person per unit time. This is measured using the human biting rate (the number of mosquitoes biting an individual over a stated period, measured directly using human baits or indirectly using light-traps, knock-down catches, baited huts, or other methods of biting rate determination) multiplied by the sporozoite rate.

- Adult mosquito density: measured by a technique previously shown to be appropriate for the vector (measured using human baits, light-traps, knock-down catches, baited huts, or other methods).

- Sporozoite rate.

Adverse events

Any indicators of adverse events of the intervention, including the following.

- Reports of poisoning in humans due to increased exposure to insecticide.

- Environmental impacts, such as changes to the biodiversity and ecosystem, due to the addition of insecticides.

Search methods for identification of studies

We attempted to identify all relevant trials, regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We searched the following databases on 18 April 2018, using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register; the Central Register of Controlled Trials (CENTRAL), published in the Cochrane Database of Systematic Reviews (Issue 4 of 12, April 2018); MEDLINE (PubMed, from 1966); Embase (OVID, from 1947); CAB Abstracts (Web of Science, from 1973); and LILACS (BIREME, from 1982). We also searched the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/), and ClinicalTrials.gov (clinicaltrials.gov/) to identify ongoing trials.

Searching other resources

Organizations (and pharmaceutical companies)

We contacted organizations, including the WHO and the Centers for Disease Control and Prevention (CDC), for ongoing and unpublished trials.

Reference lists

We also checked the reference lists of all included studies for further relevant studies.

Data collection and analysis

Selection of studies

Two review authors (JP and LC) independently screened the titles and abstracts of articles identified by the literature searches for inclusion. We assessed the full-text articles of potentially relevant trials for inclusion, using an eligibility form that was based on our inclusion criteria. We compared included trials and resolved any disagreements by discussion and consensus, with arbitration by a third review author (DM) if necessary. We ensured that we included multiple publications of the same trial only once.

Data extraction and management

Two review authors (JP and LC) independently extracted information from the included studies using pre-piloted, electronic data extraction forms. The two review authors discussed any differences in the extracted data to reach consensus, and resorted to a third review author (DM) when differences could not be resolved between them. In case of missing data, we attempted to contact the original study author(s) for clarification.

We extracted data on the following.

- Trial design: type of trial; method of participant selection; adjustment for clustering (for cRCTs); sample size; method of blinding of participants and personnel.

- Participants: trial settings and population characteristics; recruitment rates; withdrawal and loss to follow-up.

- Intervention: description of intervention (active ingredient, dose, formulation, droplet diameter, droplet density, ground or aerial spraying method, ULV or cold fogging, frequency and timing of application, size of treated area, buffer zone between clusters, caged-mosquito outcomes); co-interventions; description of control; duration of follow-up; coverage of intervention and access to co-interventions; compliance of intervention and any co-interventions.

- Outcomes: definition of outcome; diagnostic method or surveillance method; passive or active case detection; number of

events; number of participants or unit time; statistical power; unit of analysis; incomplete outcomes/missing data.

- Other:
 - primary and secondary vector(s) species; vector(s) behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic); method of mosquito collection(s); phenotypic insecticide resistance (based on WHO definitions if supplementary WHO cylinder assays or CDC bottle bioassays, or both, were performed whilst the trial was running); genotypic insecticide resistance profile (either performed during the trial or if the trial references data from previous studies done on the same local vector population within the previous five years).
 - malaria endemicity; eco-epidemiological setting; population proximity and density; *Plasmodium* species.

For dichotomous outcomes, we extracted the number of participants who experienced each outcome and the number of participants in each treatment group. If the number of participants was not reported, we estimated the treated population using census data. For count data outcomes, we extracted the number of outcomes in the treatment and control groups, and the total person time at risk in each group, or the rate ratio and a measure of variance (for example, standard error). For numerical outcomes we extracted the mean and a measure of variance (standard deviation (SD)).

For cRCTs we intended to record the number of clusters randomized; number of clusters analysed; measure of effect (such as risk ratio, odds ratio, or mean difference) with confidence intervals (CIs) or standard deviations; number of participants; and the intracluster correlation coefficient (ICC) value.

Assessment of risk of bias in included studies

We intended to independently assess cRCTs for risks of bias using the Cochrane ‘Risk of bias’ tool, and the five additional criteria listed in Section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* relating specifically to cluster-randomized trials (Higgins 2011). Two review authors (JP and LC) assessed the included non-randomized studies (NRSs) for risks of bias using the Cochrane Effective Practice and Organization of Care (EPOC) ‘Risk of bias’ tool (Cochrane EPOC 2016). We resolved any discrepancies through discussion or, if necessary, through consultation with a third review author (DM). We classified judgements of risk of bias as either at low, high, or unclear risk of bias.

Measures of treatment effect

We compared intervention and control data using risk ratios and rate ratios.

For NRSs, we intended to extract adjusted measures of intervention effects that attempted to control for confounding.

As the included ITS studies did not report intervention effect estimates that we could extract, we digitized the presented time series graphs to obtain data sets for each study using the graph digitizing software WebPlotDigitizer (automeris.io/WebPlotDigitizer). We then imported the data sets for each study into Stata version 14.1 (StataCorp 2017).

We fitted a Poisson regression model that predicted values for our outcomes of interest at the post-intervention time points in the absence of the intervention. Where the population size was reported at different time points within the time series, we included population size as an offset in the model. Where population sizes were not provided and were instead estimated using census data, we assumed that the denominator population would not have changed rapidly over short timescales, and we did not include population size as an offset in the model. The model adjusted for seasonality using a Fourier term and also accounted for overdispersion (Bernal 2017). We hypothesized that if the intervention was effective, it would have two separate effects on the outcome. The first is a step change (defined as the difference between the observed level at the first post-intervention time point and the predicted level at the same time point based on the pre-intervention trend). The second effect is a slope change (defined as the difference between the post- and pre-intervention slopes) (Ramsay 2003). For the analysis, we treated the step change and the slope change as different outcomes of the intervention. The model included terms for both the step and slope effect of the intervention, and was used to produce estimates of the step and slope rate ratios. We also produced graphs that show the observed data, the trend line fitted by the model, and the point at which the intervention was introduced.

We assessed autocorrelation for each model by examining the plot of residuals and the partial autocorrelation function. If we had identified autocorrelation we would have adjusted for this using the autoregressive integrated moving average (ARIMA) method, as in the methods of Bernal 2017. However, there was very little evidence of autocorrelation in any of our models.

We used adjusted measures of effect to summarize the treatment effect from all included NRSs. We present all results with their associated 95% CIs.

Unit of analysis issues

If we identified cRCTs that had not adjusted for clustering in the analysis, we intended to adjust data before combining them, by multiplying standard errors by the square root of the design effect (Higgins 2011). If the trial did not report the ICC value, we would have estimated the ICC from a similar trial if possible, or by searching external sources for example ICCs, or alternatively, we would not include cRCTs that had not adjusted for clustering in the meta-analysis, but would present results in a separate table.

Dealing with missing data

In case of missing data, we applied available-case analysis, only including data on the known results. The denominator is the total number of participants who had data recorded for the specific outcome. For outcomes with no missing data, we performed analyses on an intention-to-treat basis. We intended to include all participants randomized to each group in the analyses and to analyse participants in the group to which they were randomized.

Assessment of heterogeneity

We inspected forest plots for overlapping CIs and assessed statistical heterogeneity in each meta-analysis using the I^2 statistic and Chi^2 test values. We regarded heterogeneity as moderate if I^2 statistic values were between 30% to 60%; substantial if they were between 50% and 90%; and considerable if they were between 75% and 100%. We regarded a Chi^2 test statistic with a P value greater than 0.10 to indicate statistically significant heterogeneity. We explored clinical and methodological heterogeneity through consideration of the trial populations, methods and interventions, and by visualization of trial results.

Assessment of reporting biases

If there were 10 or more included trials in each meta-analysis, we intended to investigate reporting biases (such as publication bias) using funnel plots (Harbord 2006). However, we did not identify enough studies suitable for inclusion.

Data synthesis

We analysed data using Review Manager 5 (RevMan) (RevMan 2014). We intended to pool data from RCTs in a meta-analysis. If we judged NRSs were both reasonably resistant to biases and relatively homogeneous, we combined data across studies using meta-analysis (Taggart 2001). We did not include NRSs in meta-analyses with RCTs. For meta-analysis of cRCTs, if identified, we intended to use the crude or unadjusted effect estimates, while meta-analyses for NRSs used the adjusted measures of effect, as in Section 13.6.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011).

We intended to use a fixed-effect meta-analysis to combine data if heterogeneity was absent, and using a random-effects meta-analysis if considerable heterogeneity was present. However, we decided to use a random-effects meta-analysis based on the consideration of known methodological heterogeneity between the study sites. We synthesized effect estimates for the step rate ratio and slope rate ratio using the generic inverse variance method.

We used the effect estimate for the step rate ratio to estimate the immediate effect (within one post-intervention time point) of space spraying. We used the effect estimate for the slope rate ratio to estimate the effect following 12 months of space spraying. We calculated this by multiplying the risk with no space spraying by

the slope rate ratio (the proportion of cases avoided each month) for each of 12 months.

We calculated the lower limit of the CI for the risk following 12 months of spraying by multiplying the risk with no space spraying by the slope rate ratio's lower limit of the 95% CI for each of the 12 months. We calculated the upper limit of the CI for the risk following 12 months of spraying by multiplying the risk with no space spraying by the slope rate ratio's upper limit of the 95% CI for each of the 12 months.

Subgroup analysis and investigation of heterogeneity

If heterogeneity was detected between studies, we planned to perform the following subgroup analyses.

- Seasonality of malaria (perennial transmission/seasonal transmission/outbreak or high-risk settings).
- Spray equipment used: ground sprays, i.e. using hand-held or vehicle-mounted equipment, or aerial sprays.
- Time of spraying (between 7 am and 6.59 pm or 7 pm and 6.59 am).

We would have tested differences between subgroups using the Chi^2 test, with a P value of less than 0.05 indicating statistically significant differences between subgroups.

Sensitivity analysis

If possible, we intended to perform a sensitivity analysis on the primary outcome to see the effect of excluding trials at high risk of bias (for allocation concealment and incomplete outcome data) on overall results.

'Summary of findings' table

We assessed the certainty of the evidence using the GRADE approach (Guyatt 2011). We rated the certainty of the evidence for each primary and adverse event outcome, as described by Balshem 2011.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

RCTs start as high-certainty evidence but can be downgraded if there are valid reasons within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Studies can also be upgraded if there is a large effect; a dose-

response effect; and if all plausible residual confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed (Balshem 2011).

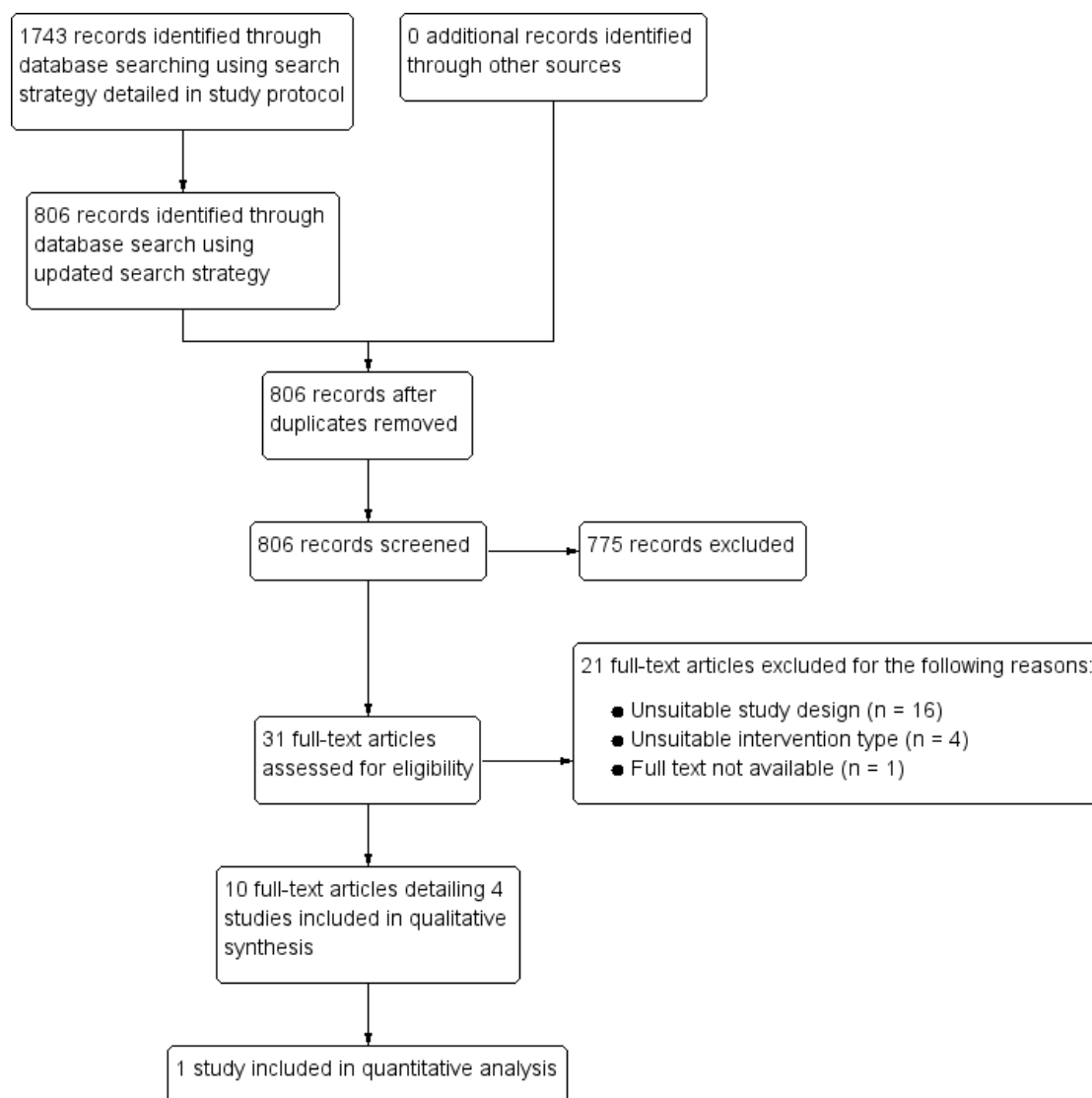
RESULTS

Description of studies

Results of the search

We identified 1743 reports through the initial electronic search. To further restrict the search, we considered only those that contained 'malaria' in either the title or abstract, reducing the total number by 937. We screened all 806 remaining abstracts against the review's inclusion criteria. Of these, we identified 31 unique reports for full-text screening. To confirm the validity of the post hoc restriction, we checked 94 of the now excluded studies (10%) against the review criteria, and included none of them. A PRISMA flowchart of the screening process is shown in Figure 2.

Figure 2. PRISMA diagram



Of the 31 unique reports identified for full-text screening, Eight reports met the inclusion criteria for the primary objective and a further two reports met the criteria for the secondary objective.

Included studies

Primary objective

We found no cRCTs for inclusion in this review.

Eight reports detailing two separate NRSs met the inclusion criteria for the review's primary outcome. Both studies met the inclusion criteria for an ITS study. Due to the nature of the intervention, it was applied to all participants within the study areas and outcomes were measured in all inhabitants of the sprayed areas. One study was conducted in the Miragoane Valley on the Southern peninsula of Haiti, with the sprayed area covering a population of 15,106 people (Krogstad 1975). The second study sprayed in three sites in the Thenpennai riverine tract in Tamil Nadu state, India (Tewari 1990). These sites were Pudupettai (Viluppuram district), Vanapuram and Melpallipattu (both Tiruvannamalai district). Due to unique challenges associated with malaria transmission in Sathanur Dam village, Vanapuram, the results from Sathanur Dam were reported separately, providing four distinct study sites.

The population size was reported for the study site of Pudupettai as 1686 people in the years 1979 to 1980 and 2145 people in 1981 to 1982. However, the population sizes were not reported for the remaining study sites in Tiruvannamalai. The number of people covered in each treatment group was therefore estimated using census data. Population sizes for each village in the study were taken from the 2011 Indian population census (COI 2011a). To account for population growth in the 30 years between the study and census dates, the population sizes were adjusted using each of the three decades' growth percentages in the district of Tiruvannamalai (SPC 2007; COI 2011b). This resulted in a reduction of 27.6% from the 2011 census data for each village. Using this method, the sizes of populations covered were estimated as 4943 (Vanapuram), 6334 (Sathanur Dam) and 5038 (Melpallipattu). Both studies reported the incidence of malaria cases. Tewari 1990 reported the incidence rate per 1000 at each site over time, with at least a year prior to space spraying implementation reported. The second study, in Haiti, did not report the incidence over time for previous years (Krogstad 1975). Where data were not provided for previous years, it was not possible to model the seasonal trend of malaria incidence in order to estimate the impact of space spraying, and we did not include the results in the meta-analysis.

No studies reported the prevalence of malaria in a time series with sufficient time points, or with a suitable control group, in order to give a contemporaneous comparison. Krogstad 1975 also provided time series data for adult mosquito density, as measured using both updraft UV light-traps and human-baited biting collections.

Both studies used malathion as the active ingredient. One study, Krogstad 1975, used an aerial delivery, spraying an ULV fog at

a dose of 4.5 oz/acre from a Beech D-18 aircraft. Spraying was conducted every 10 days. The time of spraying was not reported. The second study, Tewari 1990, used ground-based hand-held spray equipment, with distinct methods in each site. In Pudupettai, ULV fogging was conducted weekly using hand-held sprayers. After six weeks, spraying was conducted only in response to new cases. In Vanapuram (except Sanathur Dam), thermal fogging was conducted fortnightly using hand-held sprayers. Thermal fogging was conducted using jeep-mounted Tifa and handcart-mounted Tiga machines in Melpallipattu (fortnightly) and Sathanur Dam (weekly). In each site, sprays were conducted between 8 pm and 10 pm or 5 am and 7 am. Further information of the different methods used in the different sites are detailed in the [Characteristics of included studies](#) table.

In both studies, the intervention was implemented and outcomes monitored by a state malaria control programme, with support respectively from US AID (Krogstad 1975) and a local vector control research centre (Tewari 1990). Additionally, IRS was conducted as a continued co-intervention in both studies, and was implemented equally pre- and post-intervention. IRS was conducted with dichlorodiphenyltrichloroethane (DDT) in Haiti and with malathion in India. Tewari 1990 additionally listed larval habitat management and continued case management as co-interventions were also conducted during the study in the Pudupettai district.

Secondary objective

Two reports detailing a further two studies met the inclusion criteria for the review's secondary objectives. Both studies were conducted as CBA studies, with one cluster per arm.

One study was conducted in El Salvador, and used a weekly ULV spray of 5% pyrethrin with 15% piperonyl butoxide (Hobbs 1976). The insecticide was delivered using vehicle-mounted equipment, at a dose of 0.002 to 0.0025 lbs/acre, and spraying took place between 6 pm and 7pm to coincide with peak mosquito blood-seeking activity. The study was conducted by a team from the Central America Research Station (CARS). The report indicated that application of space spraying in this manner was operationally simple, and although the costs of synergized pyrethrins were high, the labour and running costs were low.

The second study was conducted in Malaysia (Seleena 2004). The team conducted a monthly ULV spray of alphacypermethrin, delivered with hand-held spraying equipment at a dose of 2 g/10,000 m². The spray team comprised villagers, who received staff training, headed by a local public health officer. Although concerns had been expressed about the practicality of ground-based space spraying in such a remote village, this approach was considered to be a practical and inexpensive solution.

Both studies reported the incidence of malaria cases and a measure of the adult mosquito density, which was reported as either the human landing rate (Seleena 2004) or the number of vectors per light-trap per night (Hobbs 1976).

Each of the four included studies is described in the [Characteristics of included studies](#) tables, and we have provided a summary of the operational details of space spraying implementation in each study in [Table 2](#).

Excluded studies

We excluded 21 full-text articles, for the following reasons (see [Characteristics of excluded studies](#)):

- 16 reports did not meet the inclusion criteria for study design

- 4 reports used an intervention that did not meet the inclusion criteria
- 1 report was not available. We considered the study unlikely to be included, as the abstract appeared to describe IRS rather than space spraying

Risk of bias in included studies

In [Figure 3](#) we give a summary of our judgement of the risks of bias in the two studies included in the primary objective. We have listed individual 'Risk of bias' assessments in the [Characteristics of included studies](#) section.

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study. We did not assess the risk of bias for [Hobbs 1976](#) or [Seleena 2004](#), as the evidence of the effectiveness of space spraying in these studies has not been presented in this review or included in the analysis.

	Was the intervention independent of other changes?	Was the shape of the intervention effect pre-specified?	Was the intervention unlikely to affect data collection?	Was knowledge of the allocated interventions adequately prevented?	Were incomplete outcome data adequately addressed?	Was the study free from selective outcome reporting?	Was the study free from other risks of bias?
Hobbs 1976							
Krogstad 1975	?	+	+	?	+	+	+
Seleena 2004							
Tewari 1990	+	+	+	?	+	-	?

It is unclear in one study whether the intervention was introduced independently from other changes that may affect the outcomes (Krogstad 1975). The effect of meteorological conditions is not explored and there is limited information on concurrent control measures such as anti-larval measures and chemotherapy. The impact of these activities is therefore hard to measure. The second study confirmed there was no change in co-interventions pre- and post-space spraying, and that the trend was observed despite normal levels of rainfall (Tewari 1990).

In both studies, the point of analysis was the point that the intervention was introduced, and data collection methods were not altered post-intervention. We rated the studies as low risk of bias for these criteria.

Due to the nature of the intervention, blinding was not conducted in either of the two studies. In both studies, the measurement of incidence depended on self-reporting of fever symptoms, which may be influenced by participant knowledge of the intervention. However, parasitaemia was confirmed by blood smear, and so we judged that there was an unclear risk of bias.

Neither of the studies was at risk of bias from incomplete outcome data. However, we judged Tewari 1990 to have a high risk of bias from selective reporting. Firstly, the study states that 24 villages in Vanapuram were sprayed, but outcome data are presented for only four of them. Secondly, the report states that mosquito density was recorded in Pudupettai, but this outcome is not reported. We also

judged this study to be at unclear risk for other potential bias, as it used a variety of spray equipment and insecticide formulations at different times and locations; these are not fully specified and it is not possible to correlate these individual interventions with the outcome data presented.

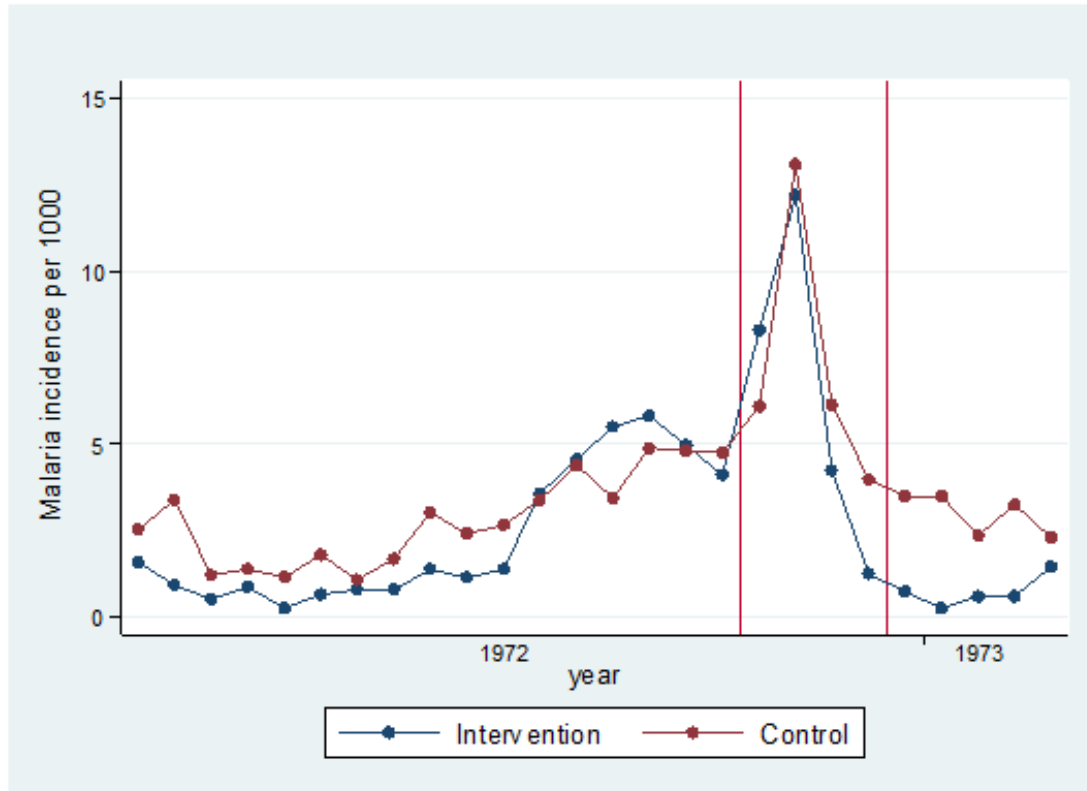
Effects of interventions

See: [Summary of findings for the main comparison](#) 'Summary of findings' table 1

Incidence

We present time series plots showing the incidence of malaria following the implementation of space spraying for each study. Figure 4 shows the incidence in the sprayed area in Haiti in comparison to equivalent data from the surrounding unsprayed area (Krogstad 1975). The incidence was reported at 17 pre-intervention time points and nine post-intervention time points. The red vertical lines indicate the initial implementation and end of the space-spraying intervention, which was timed to coincide with the peak of the transmission season. The study did not report the incidence over time for previous years. Without further information, we cannot say whether this is a typical pattern for this time of year for the intervention group or the control group, and so we have not included the results in the meta-analysis.

Figure 4. Incidence of clinical malaria per 1000 population in the Miragoane Valley of Haiti, March 1972 to February 1973. Incidence in the sprayed zone of the study site is shown in blue; the incidence in the surrounding untreated area is shown in red. The vertical red lines indicate the start and end of the space spraying intervention.



We present the observed malaria incidence in the four reported sites of [Tewari 1990](#) in Figures 5 to 8. [Figure 5](#) shows the observed incidence of malaria over time in the study site of Pudupettai. Incidence was reported at 24 pre-intervention and 24 post-intervention time points. [Figure 6](#) shows the incidence in Vanapuram (25 pre-intervention and 35 post-intervention time points). [Figure 7](#) shows the incidence in Melpallipattu (31 pre-intervention and 29 post-intervention time points), and [Figure 8](#) shows the incidence in Sathanur Dam (25 pre-intervention and 35 post-intervention time points). In each plot, the observed incidence rates are indicated by blue dots, while the red line demonstrates the trend, adjusted for seasonality. The introduction of space spraying is indicated by a vertical red line.

Figure 5. Number of cases of clinical malaria in Pudupettai, India, reported monthly between 1979 and 1982. The vertical red line indicates the start of the space spraying intervention.

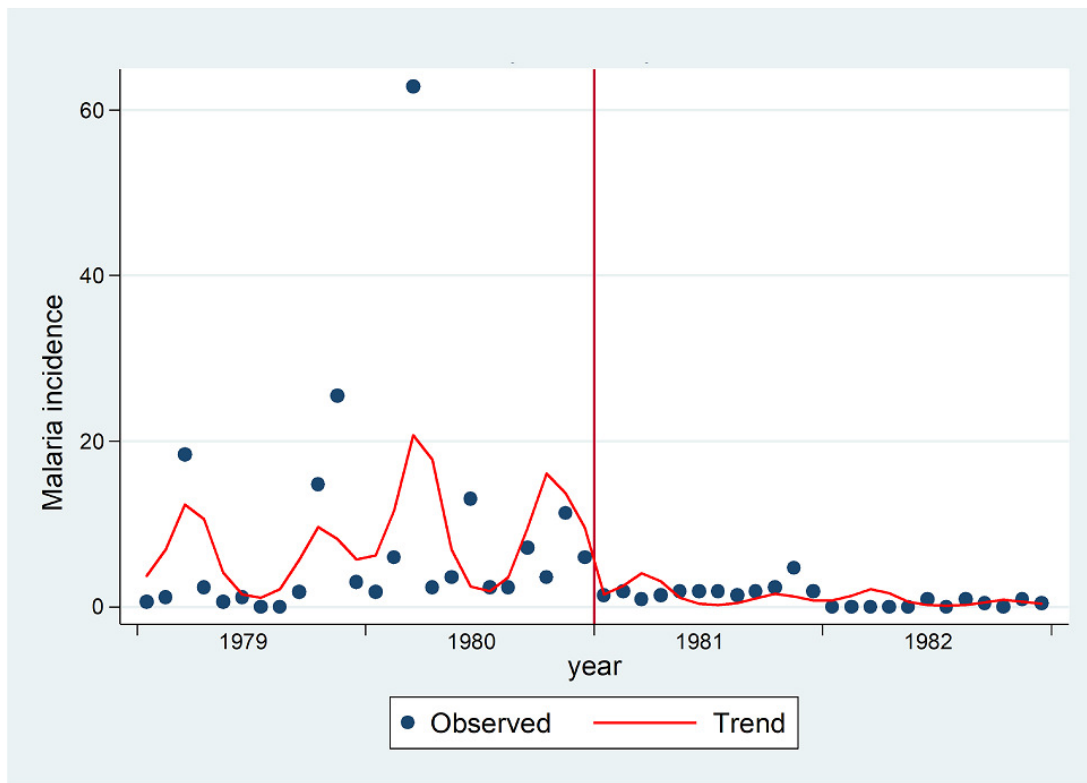


Figure 6. Number of cases of clinical malaria in Vanapuram, India, reported monthly between 1980 and 1984. The vertical red line indicates the start of the space spraying intervention.

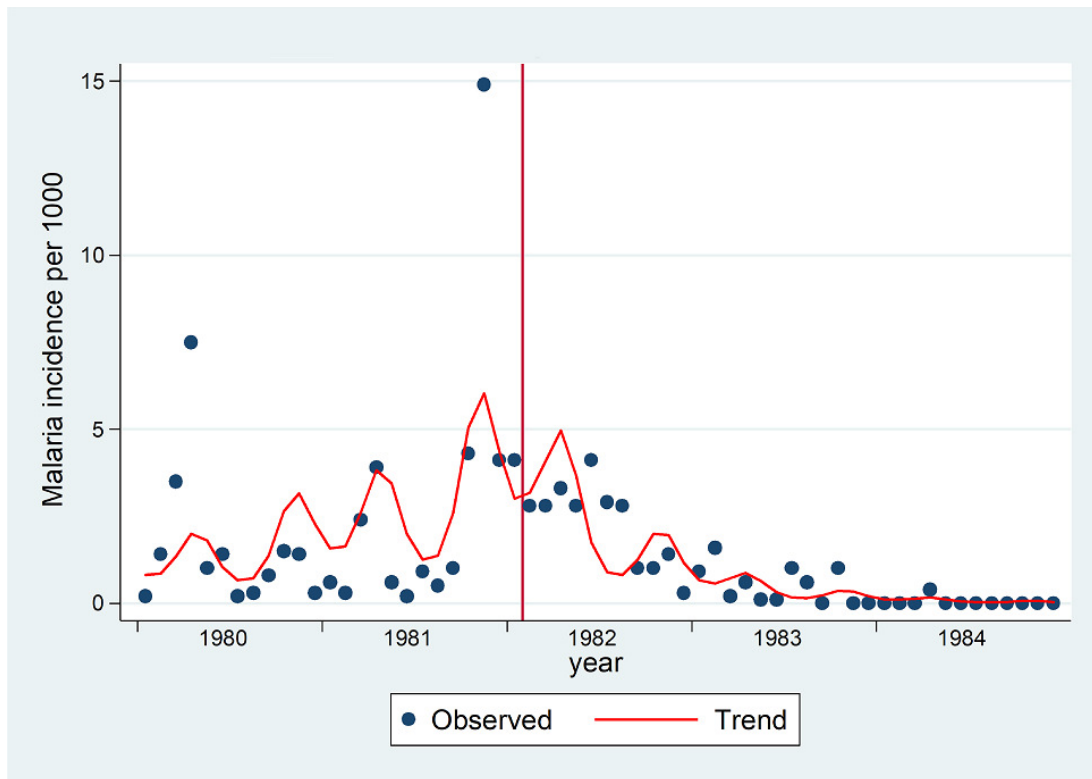


Figure 7. Number of cases of clinical malaria in Melpallipattu, India, reported monthly between 1980 and 1984. The vertical red line indicates the start of the space spraying intervention.

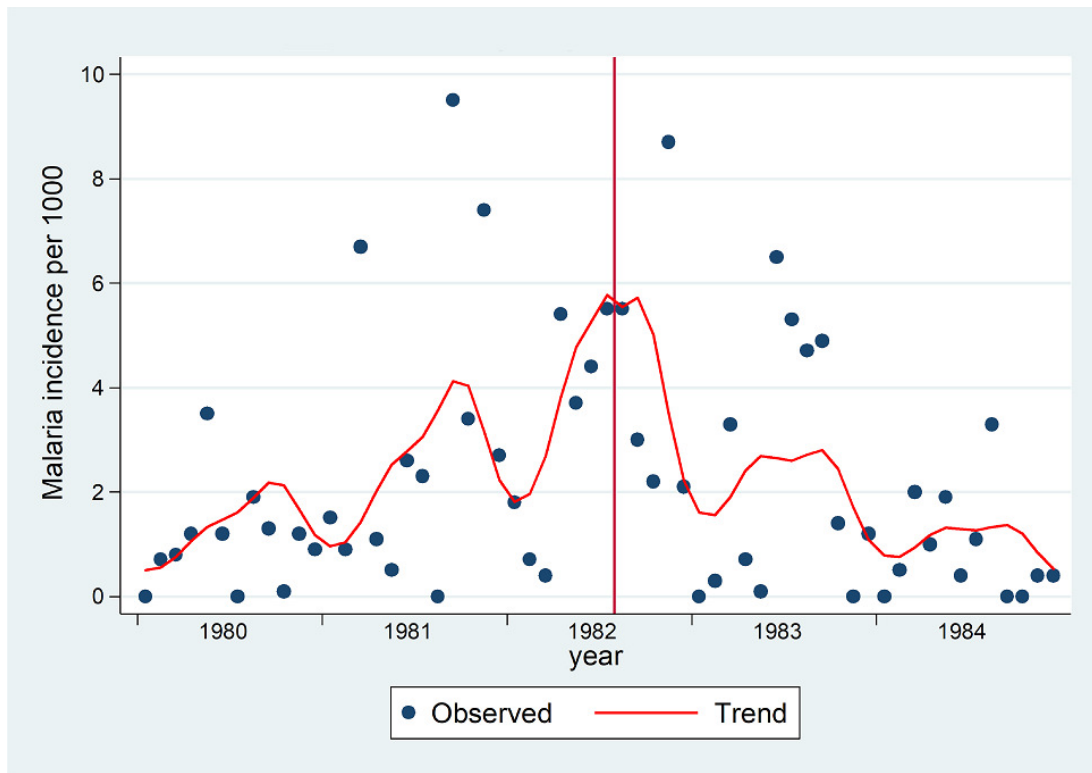


Figure 8. Number of cases of clinical malaria in Sathanur Dam, India, reported monthly between 1980 and 1984. The vertical red line indicates the start of the space spraying intervention.

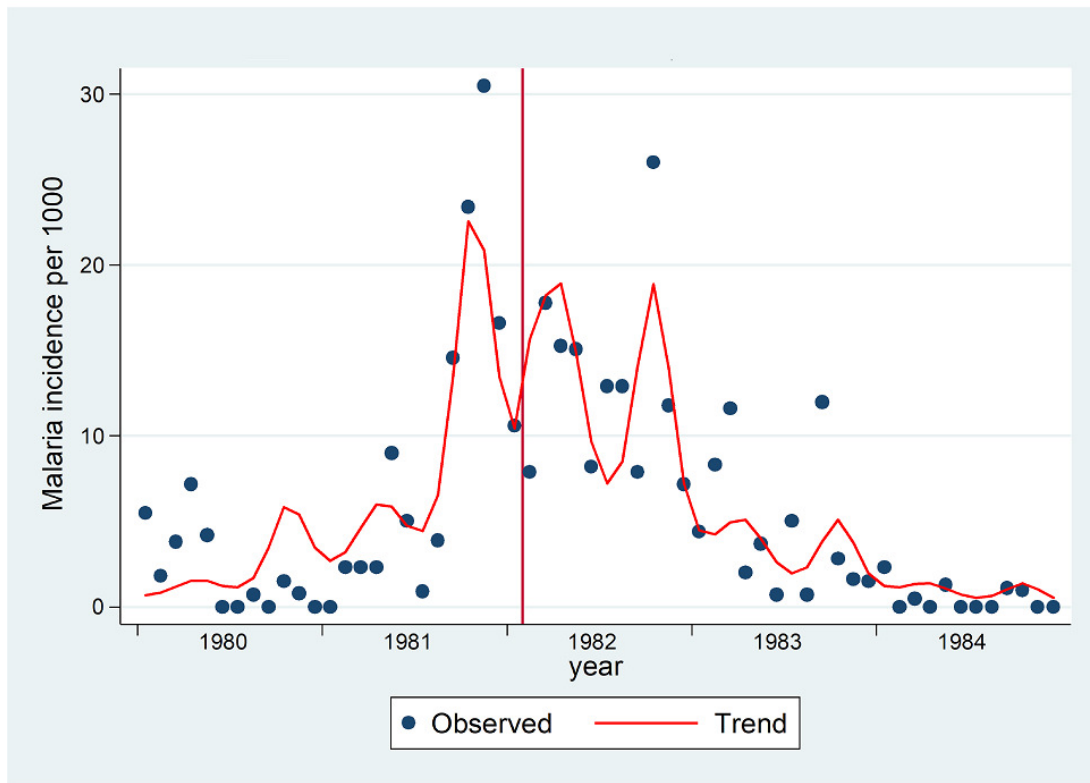
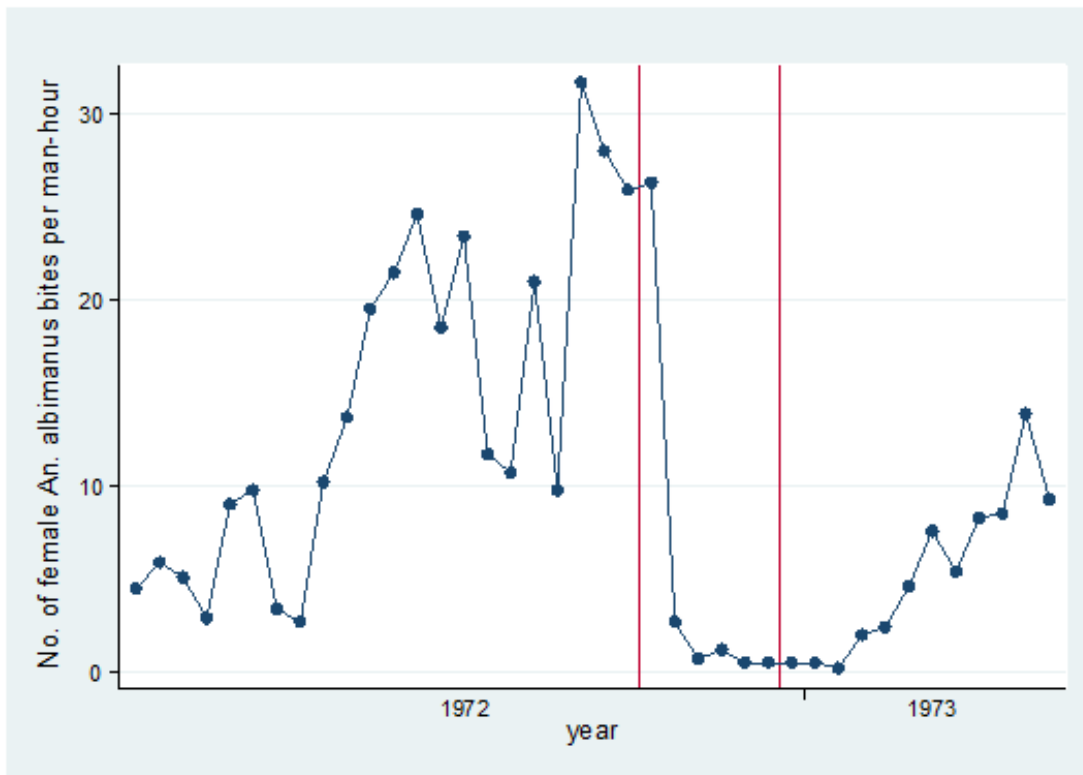


Figure 10. Mosquito density measured as a human biting rate in the sprayed region in Haiti, March 1972 to February 1973. The initial implementation and end of the space spraying intervention are illustrated by vertical red lines.



if space spraying causes a change in the slope of malaria incidence over time (RR 0.85, 95% CI 0.79 to 0.91, 1 study, very low-certainty evidence).

DISCUSSION

Summary of main results

See [Summary of findings for the main comparison](#).

Across the included studies, the incidence of malaria was the only outcome reported with a valid comparator that could be used to estimate the impact of space spraying. One study reported the monthly incidence of malaria over a four-year period, with at least one year prior and at least two years post-intervention reported (Tewari 1990). The findings of the study suggest that space spraying had an effect on the incidence of malaria. However, the certainty of the evidence is very low and we cannot be certain that the evidence provided is indicative of the true impact of space spraying on malaria incidence. We do not know if space spraying causes a step change in malaria incidence (1.00, 95% CI 0.51 to 1.92, 1 study, very low-certainty evidence). In addition, we do not know

Overall completeness and applicability of evidence

The challenges facing current malaria vector control, including the constraints of IRS and long-lasting insecticide-treated nets (LLINs) for combating residual transmission, and the emergence of pyrethroid resistance, demand the development of an expanded suite of vector control tools to meet increased global aspirations for the elimination and eradication of malaria (Gates 2015). At present, there are doubts about the practicality and effectiveness of space spraying for operational malaria control (Najera 2003). The study included in the quantitative analysis of this review provides limited evidence of the use of space spraying in specific foci of persistent and refractory malaria transmission in India. In these instances, transmission was reduced to a low level, which was subse-

quently maintained with routine interventions, without the need for regular ongoing space spray applications. However, the findings have limited applicability to global malaria control.

The study interventions included in this assessment were each conducted in Tamil Nadu state, India. The primary vector in the region is *Anopheles culicifacies*, a late-evening and night-biting mosquito. Although it is predominantly indoor-resting, outdoor resting has also been reported (Sinka 2011). There are at least 150 different malaria vector species and subspecies, and the variation in their habitats and feeding preferences is a major challenge to vector control, often requiring tailored control operations to reflect the local vector species (Ramirez 2009). In addition, local environmental conditions such as climate, vegetation and landscape can significantly impact the longevity of airborne insecticide and its ability to penetrate areas where mosquitoes are active. Due to the indirectness of these data for application to all malaria transmission settings, we expect that our estimates may be substantially different from the true magnitude of effect (Guyatt 2011). Driven in part by rapid urbanization and industrialization, the years since the studies were conducted have also seen an increase in time spent by humans outdoors, in outdoor-biting vector behaviour, and increases in vector resistance to insecticides, further reducing our certainty in the estimate of the effect for controlling malaria today (Sharma 1996).

Of the review's two primary outcomes of interest, only malaria incidence data were reported in a manner suitable for evaluation, and we are unable to report on the impact of space spraying on the prevalence of malaria. This is an important outcome that can aid the evaluation process for vector control products. New products are assessed for both efficacy and safety against established standards (WHO 2017b). Adverse event outcomes, such as ecological impacts and increases in insecticide resistance, were not reported in the included studies. However, studies into the non-target effects of space spraying for dengue control have concluded that the human health risks are most probably negligible (Peterson 2006; Schleier 2009), and that other insects with larger bodies than mosquitoes are not affected by the insecticidal sprays (Boyce 2007).

The studies included in this review were conducted in the 1970s or early 1980s, before the inauguration of LLINs as a core intervention for the prevention of malaria, and its resulting decrease in malaria incidence (21%) and malaria-related deaths (29%) between 2010 and 2015 (WHO 2016a). The studies therefore have limited applicability in the current landscape of global malaria control. As ensuring universal coverage with LLINs or IRS for all people at risk of malaria forms Pillar 1 of the Global Technical Strategy for Malaria, there is a question about the effectiveness of space spraying as a complementary measure to LLINs that remains unanswered by the evidence in this review (WHO 2016a).

Certainty of the evidence

In the GRADE approach to assessing the certainty of evidence, RCTs are considered to provide high-certainty evidence, assuming they are free from important limitations and bias. Due to the inherent biases in the design of NRSs, evidence provided by ITS studies, such as those reported here, is considered to be of low certainty, even without further limitations (Balslem 2011). We have further downgraded the certainty of our findings for several reasons.

Firstly, we rated the included studies at serious risk of bias. In particular, we considered the risk of selective reporting and the lack of clarity over the independence of the intervention likely to lower confidence in the estimate of the effect. We also downgraded the certainty for serious indirectness due to the restricted range of included studies and the substantial differences in effectiveness that may be expected in other malaria transmission settings with different environments and primary vector species, as described above (Guyatt 2011).

We also judged the certainty of the estimate of the step rate ratio to be at serious risk of imprecision, as the CI for the estimate included both a sizeable increase and a decrease in the incidence trend of malaria. Overall, we graded the certainty of the evidence as very low, so that we have very little confidence in the effect estimates. We present full details of the GRADE assessment in the [Summary of findings for the main comparison](#).

Potential biases in the review process

One potential source of bias in the review process was the decision to include NRSs, which are themselves likely to contain greater biases than randomized trials. The results from such studies should therefore be interpreted with caution. To account for this, we used an adapted 'Risk of bias' tool including extra criteria for issues specific to NRSs, and we have downgraded the certainty of our overall estimates of the effect. A risk to the complete collation of studies meeting the inclusion criteria is that we could not retrieve a potentially relevant study, although we considered it unlikely to be included from the title and abstract screening stage. Regarding the analysis, the exact number of cases per time point was not reported in a table or the text, which required us to estimate the figures used in the review analysis using a plot digitizer. This may introduce small inaccuracies. In addition, as treated population sizes were not reported for each site, we had to estimate the population sizes in included villages using census data which were adjusted for population growth. However, these inaccuracies are not expected to lead to over- or under-estimation of malaria incidence that is differential between pre- and post-intervention timepoints. Finally, our model identified an upward pre-intervention trend in malaria incidence in the absence of space spraying in four out of the five study areas. It is possible that in some of these cases the second pre-intervention year had a higher incidence than the first, due to chance. With the analysis methods used in this review, this

would result in an inaccurate estimation of the pre-intervention slope and consequent overestimation of the post-intervention effect. Access to data covering more years would improve our confidence in the estimates of effect.

Agreements and disagreements with other studies or reviews

To the best of our knowledge, this is the first systematic review to evaluate the impact of space spraying on malaria transmission. However, the conclusions are similar to those in a review of space spraying's impact on dengue transmission. As in our review, [Esu 2010](#) used reduced thresholds for study design inclusion criteria, due to concerns about identifying an adequate number of robust studies. Only one study, which was confounded by co-interventions and lacking a control group, reported the impact on dengue incidence. This finding further highlights the lack of high-quality studies that have been conducted to assess the effectiveness of space spraying for disease control, and the need for more robust evidence to support decision-making on space spraying implementation.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence-based policy-making is an imperative process for the development of vector control global guidelines. This review identifies an absence of evidence of space spraying's impact on malaria prevalence, and we are very uncertain about the estimate of the effect on malaria incidence. Consequently, there is an insufficient evidence base for policy-makers to adjudge whether or not space spraying has an impact on malaria morbidity.

Implications for research

This review highlights the lack of well-designed trials of space spraying as a malaria prevention tool. Common issues surrounding trial designs included a lack of a contemporaneous control group, or study arms consisting of one cluster only. Trials identified in this review often had unclear descriptions of the delivery of co-interventions, particularly IRS and larval source management. It is important that any future research adequately reports on and controls for coverage of these interventions. In order to demonstrate value for public health, future trials should report on epidemiological outcomes in addition to entomological outcomes. [Wilson 2015](#) provides further guidance on improving the design and reporting of vector control trials to meet the demands of evidence-based policy making.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hobbs 1976

Methods	<p>Study design: controlled before-and-after (CBA) study</p> <p>Unit of allocation: village (Cangrejera village chosen as intervention village due to house accessibility by road; the nearby Melara village was selected as the control village due to its similar housing, agricultural practices and vector density)</p> <p>Number of units: 1 : 1</p> <p>Outcome assessment/surveillance type: passive case detection through local collaboration centres, where suspected cases could report and a blood smear would be taken. This has previously been shown to be a sensitive surveillance method. Mosquito densities were measured using New Jersey light traps 1 night per week.</p> <p>Adjustment for clustering: none</p>
Participants	Number of participants: 408:485
Interventions	<p>Active ingredient and dosage: pyrethrin, 0.002 to 0.0025 lbs per acre</p> <p>Formulation: 5% pyrethrin synergized with 15% piperonyl butoxide</p> <p>Droplet density: not described</p> <p>Droplet diameter: not described</p> <p>Thermal/Cold (ULV) fog: ULV</p> <p>Ground/Aerial: Ground, using truck-mounted sprayer</p> <p>Frequency of spraying: weekly, for 4 months (1st week May - last week August 1974, coinciding with the peak malaria transmission season)</p> <p>Time of spraying: 6pm - 7pm, to coincide with activity of female <i>An albimanus</i></p> <p>Size of treated area: not described</p> <p>Buffer size between clusters: 3 km</p> <p>Caged mosquito outcomes: 81.5 - 100.0% mortality (0.0 - 15.6% in control)</p> <p>Control: no space spraying</p> <p>Co-interventions (type, access, compliance): not described</p>
Outcomes	<p>Outcomes measured:</p> <ul style="list-style-type: none"> • number of cases of <i>Plasmodium falciparum</i> malaria • <i>An albimanus</i> density <p>Length of follow-up: 15th June to 15th September (both in 1973, pre-spray, and 1974, during the intervention)</p>
Location Profile	<p>Study location: villages in the coastal plain east of La Libertad, El Salvador</p> <p><i>Plasmodium</i> species: <i>falciparum</i> and <i>vivax</i></p>
Vector Profile	<p>Primary vector species: <i>An albimanus</i></p> <p>Phenotypic resistance profile: moderately to highly resistant to dichlorodiphenyltrichloroethane (DDT), dieldrin, malathion, and propoxur</p> <p>Method of mosquito collection: mosquito densities were measured using New Jersey light-traps 1 night a week, from sunset until sunrise. Densities were measured the night before a spray round</p>
Notes	<p>CBA; not included in the meta-analysis</p> <p>Funding source: unknown</p> <p>Potential conflicts of interest: none known</p>

Methods	<p>Study design: interrupted time series (ITS) (though other designs were also used within the study) to assess the impact of space spraying in an area on epidemiological, entomological and ecological outcomes. For some outcomes, the surrounding unsprayed area was reported as a comparison. The malaria incidence rate and adult mosquito density were the only outcomes meeting the study design criteria for this review.</p> <p>Unit of allocation: N/A</p> <p>Number of units: 1</p> <p>Outcome assessment/surveillance type: incidence of malaria assessed using a combination of active case detection (paid workers visiting each house in the area once every 2 weeks; blood smears were examined for all residents reporting malaria symptoms) and passive case detection (blood smears examined for those reporting to voluntary collaborators with malaria symptoms). Mosquito density and biting rates measured using updraft UV light-traps and human-baited biting collections</p> <p>Adjustment for clustering: none</p>
Participants	<p>Number of participants: 15,106 living in sprayed area (31,710 including unsprayed area)</p> <p>Population characteristics: of the 31,710, 39% < 15 years old</p>
Interventions	<p>Active ingredient and dosage: malathion 95%, 6 oz per acre for first cycle and 4.5 oz per acre for all subsequent cycles</p> <p>Formulation: not described</p> <p>Droplet density: 20 - 47 droplets per square inch</p> <p>Droplet diameter: 40 - 50 µm (open sites) and 25 - 40 µm (protected sites)</p> <p>Thermal/Cold (ULV) fog: ULV</p> <p>Ground/Aerial: aerial (Beech D-18 aircraft equipped with 2 x 65-gallon fibreglass spray tanks. Flat fan 8002E spray nozzles were installed beneath the wings facing 45 °down and forward). The aircraft was flown at a speed of 140 mph and an altitude of 150 feet</p> <p>Frequency of spraying: every 10 days, with an extra application 5 days after the initial spray. 6 applications were made over a 45-day period</p> <p>Time of spraying: not reported</p> <p>Size of treated area: 20,000 acres</p> <p>Buffer size between clusters: N/A</p> <p>Caged mosquito outcomes: caged mosquitoes in the sprayed area showed 100% mortality within 2 hours after spraying</p> <p>Control: N/A</p> <p>Co-interventions (type, access, compliance): IRS with DDT</p>
Outcomes	<p>Epidemiological outcomes measured:</p> <ul style="list-style-type: none"> ● incidence of malaria ● slide positivity rate <p>Entomological:</p> <ul style="list-style-type: none"> ● adult mosquito density (measured using both light-traps and human baits) <p>Ecological (note- not following suitable study design for inclusion in review):</p> <ul style="list-style-type: none"> ● bird abundance ● AChE levels in bats, birds, lizards and fish <p>Length of follow-up: 5 months (October 1972 - March 1973). Sprays were scheduled to begin when epidemic levels were reached (100 cases/month/10,000 population)</p>

Krogstad 1975 (Continued)

Location Profile	Study location: Miragoane Valley, southern peninsula, Haiti. The area has a natural barrier of mountain ranges which were expected to limit immigration of mosquitoes from adjacent unsprayed areas Malaria endemicity: perennial and seasonal with persistent pattern of outbreaks, from October into January
Vector Profile	Primary vector species: <i>Anopheles albimanus</i> Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic): breed in marshes surrounding shallow lakes in the valley floor. Adults rest in dense sugar canes and banana groves Phenotypic resistance profile: susceptible to malathion (in preliminary tests: 92% mortality at 0.8% malathion, 100% mortality at 1.6% malathion. 0% mortality in controls) Method of mosquito collection: 9 updraft UV light-traps at 3 collection sites, operating from 5.30pm to 5.30am Human-baited biting collections measured over 1 hour at 2 locations in each of the 3 collection sites (1 near breeding sites and 1 near houses)
Notes	Funding source: unknown Potential conflicts of interest: none known

Risk of bias

Bias	Authors' judgement	Support for judgement
Was the intervention independent of other changes?	Unclear risk	There is a lack of detail of concurrent control measures such as IRS, and environmental factors such as rainfall; the impact of these is therefore hard to measure
Was the shape of the intervention effect pre-specified?	Low risk	The point of the analysis is the point of the intervention
Was the intervention unlikely to affect data collection?	Low risk	The sources and methods of data collection were the same before and after the intervention
Was knowledge of the allocated interventions adequately prevented?	Unclear risk	Unlikely that the outcomes were assessed blindly. Incidence measurements depended on self-reporting of fever symptoms that may be influenced by participant knowledge of the intervention, although parasitaemia was confirmed by blood smear. Mosquito density measurements were objective and unlikely to be influenced by this knowledge
Were incomplete outcome data adequately addressed?	Low risk	No missing outcome data likely to bias the results

Krogstad 1975 (Continued)

Was the study free from selective outcome reporting?	Low risk	The study design states that vector densities were also recorded in unsprayed areas but these are not reported. This may show a reduction in densities for reasons other than spraying. However, as time series data were used for this outcome, we did not consider this selective reporting likely to cause a bias in the results reported in this review
Was the study free from other risks of bias?	Low risk	There is no evidence of other risk of biases

Seleena 2004

Methods	<p>Study design: CBA study with 4 treatment arms:</p> <ul style="list-style-type: none"> • space spraying with chemical adulticide • space spraying with biological larvicides • space spraying of both chemical adulticide and biological larvicides • untreated control arm <p>Unit of allocation: village Number of units: 1:1:1:1 Outcome assessment/surveillance type: Incidence rate was monitored by passive (through the Ranau health office) and active case detection (through monthly mass blood surveys covering ~70% of the population) Mosquitoes were monitored using bare leg catches. The infectious status of the female anophelines was determined by microscopic examination Adjustment for clustering: none</p>
Participants	<p>Number of participants: 178 (intervention); 216 (control). A further 285 participants were included in the remaining arms of the study not relevant to this review Population characteristics: not described</p>
Interventions	<p>Active ingredient and dosage: alphacypermethrin, 2 g AI/10⁴ x m² Formulation: alphacypermethrin (Fendona SC/Fendona 10SCR) was mixed with sieved stream water Droplet density: not described Droplet diameter: 111.0 μm to 191.0 μm Thermal/Cold fog (ULV): ULV Ground/Aerial: ground, with hand-held sprayers Frequency of spraying: monthly Time of spraying: not described Size of treated area: not described Buffer size between clusters: at least 3.5 to 6.0 km Caged mosquito outcomes: not described Control: no space spraying of adulticide or larvicide Co-interventions (type, access, compliance): IRS and the use of insecticide-impregnated mosquito nets (lambda-cyhalothrin and deltamethrin nets)</p>

Outcomes	<p>Outcomes measured:</p> <ul style="list-style-type: none"> ● number of reported malaria cases ● <i>An balabacensis</i> human landing rate ● <i>An balabacensis</i> parity rate ● <i>An balabacensis</i> infection rate ● slide positivity rate ● larval mortality of <i>Ae. aegypti</i> and <i>Culex quinquefasciatus</i> <p>Length of follow-up: 2 years. Spraying from November 1998 until December 1999, with further spraying monthly from March 2000 to August 2000</p>
Location Profile	<p>Study location: Ranau District, Sabah State, situated in the north of Borneo Island, Malaysia</p>
Vector Profile	<p>Primary vector species: <i>Anopheles balabacensis</i> Secondary: <i>An sundaicus</i> and <i>An flavirostris</i> Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic): Exophilic and exophagic behaviour (up to 27 times more bites outside than inside). Early biting from 18.00 Phenotypic resistance profile: susceptibility tests have shown the anopheline mosquitoes have resistance to 4% DDT and 0.75% permethrin. Female mosquitoes in Sabah have also been demonstrated to avoid walls treated with DDT for a period of 3 - 4 months after an IRS treatment Method of mosquito collection: mosquitoes were caught outdoors using the bare leg catch technique from 18.00 to 24.00 hrs. Surveillance was conducted 2 days before spraying, (about 4 weeks after the previous spray), except for June to August 2000, which was conducted 2 weeks after the previous spray, to correlate the effectiveness of the spraying with the mosquito life cycle</p>
Notes	<p>CBA; not included in the meta-analysis Funding source: Malaysian government and Valent Biosciences Potential conflicts of interest: none known</p>

Methods	<p>Study design: ITS (though other designs were also used within the study) to assess the impact on epidemiological and short-term entomological outcomes, following spraying with a variety of equipment and formulations. For some outcomes, nearby unsprayed areas are reported as a comparison. In Pudupettai, however, the control group was contaminated as it received space spraying 3 times, and because there was only 1 cluster in this arm, the control group is not a valid comparison. The malaria incidence rate is the only outcome that meets the study design criteria for this review.</p> <p>Unit of allocation: N/A Number of units: N/A</p> <p>Outcome assessment/surveillance type: routine surveillance and treatment carried out by the State National Malaria Programme. Incidence rate was monitored through fever surveillance conducted at fortnightly intervals in 6 villages - Porasapattu and Pudur (Pudupettai PHC), Agarampallipattu, Edathanur, Kolamanjanur and Sathanur Dam (Vanapuram PHC), selected on the basis of a high incidence of malaria (API ranging from 25.4 - 105.9) Fever cases led to a blood smear examination. Mass blood surveys were carried out in 11 villages, including the index villages, in March - April and again in October - November of each year of the study</p> <p>Adjustment for clustering: none</p>
Participants	<p>Number of participants: the population receiving the intervention is not reported. For the analysis, we have estimated population sizes using census data</p>
Interventions	<p>A variety of formulations and spraying machines were used in the course of the study to measure each one's impact on entomological outcomes.</p> <p>Pudupettai: Active ingredient and dosage: malathion, 325 - 375 mL per hectare Formulation: technical grade malathion Droplet density: N/S Droplet diameter: 27.1 - 28.6 µm Thermal/cold (ULV) fog: ULV Ground/aerial: Ground spraying, using 2 different hand-held sprayers Frequency of spraying: fortnightly Caged mosquito outcomes: 83.5% - 96.2% indoor mortality. 55.1% - 81.1% outdoor mortality < 50 m</p> <p>Vanapuram (except Sanathur Dam): Active ingredient and dosage: malathion, 150 mL per hectare Formulation: 5% technical grade malathion in diesel Droplet density: N/S Droplet diameter: 37.4 µm Thermal/cold (ULV) fog: thermal Ground/aerial: ground spraying, using Enfog hand-held sprayer Frequency of spraying: fortnightly Caged mosquito outcomes: 88.5% - 92.4% indoor mortality. 31.3% outdoor mortality < 50 m</p> <p>Melpallipattu (and Sanathur Dam): Active ingredient and dosage: malathion, 263 - 300 mL per hectare Formulation: 5% technical grade malathion in diesel (and in some cases 10%) Droplet density: N/S Droplet diameter: 22.7 - 65.7 µm</p>

	<p>Thermal/cold (ULV) fog: thermal</p> <p>Ground/aerial: ground spraying, using jeep-mounted Tifa and handcart-mounted Tiga machines</p> <p>Frequency of spraying: fortnightly (except Sanathur Dam: weekly, due to village's specific problems)</p> <p>Caged mosquito outcomes: 60.4% - 100% indoor mortality. 74.1% - 98.4% outdoor < 250 m</p> <p>Time of spraying: 2000 hr - 2200 hr, and 0500 hr - 0700hr.</p> <p>Size of treated area: N/S</p> <p>Buffer size between clusters: N/A</p> <p>Control: N/A</p> <p>Co-interventions (type, access, compliance): residual spraying with malathion conducted 3 times each year (April - May, July - August and September - October)</p>
Outcomes	<p>Outcomes measured:</p> <ul style="list-style-type: none"> ● incidence of malaria ● prevalence (no measurements recorded prior to intervention, or in control area) ● slide positivity rate ● <i>An culicifacies</i> density - (indoor/outdoor resting rates and biting rate) - (Measurements before and after a single spraying cycle) ● parity ● sporozoite rate <p>Length of follow-up: 4 years (January 1981 - December 1984). Spraying operations were conducted in</p> <ul style="list-style-type: none"> ● 2 villages in Pudupettai (February 1981 - December 1982) ● 24 villages in Vanapuram (February 1982 - December 1984) ● 3 villages in Melpallipattu (August 1982 - December 1984)
Location Profile	<p>Study location: 3 sites along the Thenpennai riverine tract in Tamil Nadu state, India. These are Pudupettai (then South Arcot district; now Viluppuram district), Vanapuram, and Melpallipattu (then North Arcot district, now Tiruvannamalai district). Due to the unique epidemiological challenges of malaria transmission in Sathanur Dam village in Vanapuram, the results from Sathanur Dam are reported separately to Vanapuram, providing 4 distinct study sites</p> <p><i>Plasmodium</i> species: 73.1% <i>vivax</i>, 21.5% <i>falciparum</i>, 5.4% mixed</p>
Vector Profile	<p>Primary vector species: <i>An culicifacies</i></p> <p>Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic): Shows some exophilic behaviour</p> <p>Phenotypic resistance profile: resistant to DDT. Susceptible to malathion</p> <p>Method of mosquito collection: indoor/outdoor timed resting catches (days 1, 2, 3 and 11 after each spray), and indoor/outdoor all-night human baited collections (day 3 after spraying)</p>
Notes	<p>Funding source: unknown</p> <p>Potential conflicts of interest: none known</p>
Risk of bias	

Bias	Authors' judgement	Support for judgement
Was the intervention independent of other changes?	Low risk	The concurrent IRS rounds were conducted in the same way as previous years and so would not explain a change in trend. The possibility that the decline was caused by lower than average rainfall in 1982 is unlikely, as villages sprayed in 1981 saw a decline in the same year, and the downward trend continued despite normal to heavy rainfall in 1983 and 1984
Was the shape of the intervention effect pre-specified?	Low risk	The point of analysis is the point of the intervention
Was the intervention unlikely to affect data collection?	Low risk	The methods of data collection were the same before and after the intervention
Was knowledge of the allocated interventions adequately prevented?	Unclear risk	Unlikely that the outcomes were assessed blindly. Incidence measurements depended on self-reporting of fever symptoms that may be influenced by participant knowledge of the intervention, although parasitaemia was confirmed by blood smear
Were incomplete outcome data adequately addressed?	Low risk	No missing outcome data likely to bias the results
Was the study free from selective outcome reporting?	High risk	The report states that 24 villages in Vanapuram were sprayed but a time series of the number of cases and slide positivity rate is only presented for 4 of these villages
Was the study free from other risks of bias?	Unclear risk	A variety of spray equipment and formulations are used and is unclear at which times and locations each has been used

Abbreviations: AI: active ingredient; CBA: controlled before-and-after; DDT: dichlorodiphenyltrichloroethane; ITS: interrupted time series; N/A: not applicable; N/S: not stated.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adam 1964	Did not meet inclusion criteria for study design. The report documents a control campaign using multiple vector control activities undertaken simultaneously including indoor spraying, larviciding, drainage and destruction of potential breeding sites, as well as outdoor spraying. The campaign did not compare an intervention area with an untreated control group or provide a time series with data points prior to the intervention
Afridi 1962	Did not meet inclusion criteria for study design. The report is not a trial, rather a history of the medical services of the Indian Armed Forces in the Second World War, including malaria control alongside other medical services such as nutrition and disease prevention. The two main methods described for controlling malaria were residual spraying with dichlorodiphenyltrichloroethane (DDT) and drug prophylaxis, adding to previous methods of larviciding and larval habitat modification
Bown 1981	Did not meet inclusion criteria for intervention type. The study compared a village receiving ULV application with technical-grade malathion with a village receiving no intervention. However, applications of malathion were both indoor and outdoor, and therefore the intervention is not suitable for inclusion in the review. The study also reported no epidemiological outcomes, only entomological indices (adult landing rates, resting densities, and ovitrap recordings)
Cáceres G 2013	Did not meet inclusion criteria for intervention type. The report documents the response to an epidemic of malaria in Venezuela in 2002. The country reported the highest recorded incidence of malaria in its history with 51,264 cases, surpassing the previous high of 5893 in 1990. The primary intervention used was preventive treatment by mass drug administration using 'cloroquinine' and 'primaquinine'. This intervention was supplemented with space spraying. There was no control group for the intervention
De Andrade 1986	Did not meet inclusion criteria for study design. The paper documents the response to an outbreak of malaria in São Paulo State of Brazil in 1984. It is not a trial and has no control group. Space spraying is conducted using DDT. The report documents the treatment of the cases
Escudie 1963	Did not meet inclusion criteria for intervention type. The intervention tested in the study was a residual insecticide dispenser which was placed within study houses, and dispensed dichlorvos insecticide. One study village was compared against one control village where houses did not receive dichlorvos dispensers. Blood samples were drawn from all children up to 10 years old for smear and thick blood film examinations, once before and seven times after dichlorvos treatment
Harper 1947	Did not meet inclusion criteria for study design. The report is not a trial, rather a history of the control methods employed to prevent malaria and other tropical diseases in the Second World War, South Pacific Campaign (1942 - 1945). A number of interventions are described that were employed simultaneously, including careful choice of camp sites, habitat modification, larviciding from the ground (paris-green dust, oil and later DDT solution or dust) or from aircraft (DDT solution), space spraying with pyrethrum aerosols and residual DDT preparations, impregnating bed nets, screening, semi-permanent and permanent control work and suppressive medication
Mason 1977	Did not meet inclusion criteria for study design. The report documents the incidence of malaria and density of the primary vector species in a coastal region of El Salvador, over a period in which several interventions were implemented in the study area. These included aerial application of the larvicide Abate, two cycles of mass drug distribution with amodiaquine, and one application cycle of the residual insecticide propoxur, applied to the exterior walls of each house in the area. The report is not a clinical trial and no control group was examined

(Continued)

Prasad 1992	Did not meet inclusion criteria for study design. The report documents the slide positivity for malaria and density of the vector species in Farukkhabad district, India, over a period in which several interventions were implemented in the study area. These included indoor residual spraying (IRS) with DDT, space spraying with 5% or 6% malathion, larviciding with Baytex, and mass drug administration with chloroquine, primaquine, and metakelfin. The report is not a clinical trial and no control group was examined
Shalli 1970	Did not meet inclusion criteria for study design. The report documents the success of a control programme in Basrah Liwa, Iraq, as it replaced DDT for use in IRS with malathion in some areas, where high resistance to DDT was detected alongside susceptibility to malathion. During the study, high amounts of flooding contributed to higher than usual transmission of the disease. To combat this, a range of measures were introduced, including space spraying with diazinon, intensified larviciding measures, aerial spraying with DDVP, and mass drug administration. The report is not a clinical trial and no control group was examined
Sharma 1986	Did not meet inclusion criteria for study design. The study evaluated the impact of space spraying on lab-reared caged mosquitoes only, which were placed at different sites in a region sprayed with malathion. The report is not a clinical trial and no control villages were studied, although control caged mosquitoes were monitored, in cages placed outside of spraying areas
Strickman 2001	Did not meet inclusion criteria for study design. The report documents the incidence of malaria and density of the primary vector species in a military camp in South Korea, over a period in which several interventions were implemented in the study area. These included personal protection such as topical repellents, permethrin-treated clothing and mosquito nets, window screens, indoor spraying with permethrin, and ULV space spraying with piperanyl butoxide. The report is not a clinical trial and no control group was examined
Turner 1977	Did not meet inclusion criteria for study design. The impact of ULV using malathion, delivered using vehicle-mounted Leco machines (where villages were accessible by road) and hand-held Fontan sprayers (where villages were not accessible by road) on mosquito density was evaluated in the Solomon Islands No control group was monitored. Two outcomes were monitored: the man-biting rate, and mosquito sensitivity to spraying (using caged mosquitoes caught in the previous nights' man-biting collections). Man-biting rates were recorded before, during, and several days after spraying. Without three time points prior to the intervention implementation, the study did not meet the criteria for an ITS study
Viswanathan 1950	Did not meet inclusion criteria for study design. The report is not a trial, but summarizes the actions of the Bombay State malaria organization set up in 1942 and its impact on malaria transmission and vector populations. The paper describes the range of interventions that have been used including drug administration, mosquito larvicides, habitat modification and space spraying, before the introduction of IRS with DDT
Warren 1985	Did not meet inclusion criteria for intervention type. The report is an investigation into the impact on sprayers' (i.e. those who have carried out IRS in a trial in Haiti) urinary metabolites and blood cholinesterase levels
Zapata 1953	Full text was not available. We consider the study unlikely to be included, as the abstract appears to describe IRS (though published before the term was commonly used) rather than space spraying

Abbreviations: DDT: dichlorodiphenyltrichloroethane; IRS: indoor residual spraying.

DATA AND ANALYSES

Comparison 1. Space spraying versus no space spraying

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of malaria (step rate ratio: indicating the impact of space spraying at the first pre-intervention time point)	1		Rate Ratio (Random, 95% CI)	1.00 [0.51, 1.92]
2 Incidence of malaria (slope rate ratio: indicating the proportion of cases reduced per post-intervention time point)	1		Rate Ratio (Random, 95% CI)	0.85 [0.79, 0.91]

ADDITIONAL TABLES

Table 1. WHO-recommended insecticides for space spraying against mosquitoes

Compound and formulation	Concentration (g AI/ha)	
	Cold fog	Thermal fog
Deltamethrin ULV	0.5 to 1.0	0.5 to 1.0
Deltamethrin EW	1.0	-
Lambda-cyhalothrin EC	1.0 to 2.0	2.0
Malathion EW and ULV	112 to 600	112 to 600
d-d, trans-cyphenothrin EC	3.5 to 4.0	3.5 to 4.0

Abbreviations: EC: emulsifiable concentrate; EW: emulsion, oil in water; ULV: ultra-low volume liquid; AI: active ingredient

Table 2. Operational characteristics of studies

Study	Active ingredient/formulation/dose	Delivery method	Frequency and timing of application	Who implemented the intervention	Vector species
Haiti (Krogstad 1975)	Malathion 95% <ul style="list-style-type: none"> • ULV fog • 6 oz/acre (1st) 	Aerial (Beech D-18 aircraft)	Every 10 days Extra application 5 days after the initial	The Service National d'Éradication de	<i>An albimanus</i>

Table 2. Operational characteristics of studies (Continued)

	cycle) <ul style="list-style-type: none"> • 4.5 oz/acre 		spray Time of spraying: not stated	la Malaria (SNEM) , supported by US-AID	
India (Tewari 1990)	Malathion <ul style="list-style-type: none"> • ULV and thermal • dose varied depending on sprayer (150 to 375 mL/ha) See Characteristics of included studies for further details	Ground (hand-held Fontan and Enfog sprayers, jeep-mounted Tifa machines and hand-cart-mounted Tiga machines	In Pudupettai, spraying was conducted weekly for 6 rounds, and subsequently applied in response to new cases or increases in vector density. In Vanapuram and Melpallipattu spraying was conducted fortnightly, in all but one village (Sathanur Dam) where spraying was conducted weekly Time of spraying: 8pm - 10pm and 5am - 7am	State National Malaria Elimination Programme (NMEP), with guidance from the Pondicherry Vector Control Research Centre	<i>An culicifacies</i>
El Salvador (Hobbs 1976)	5% pyrethrin with 15% piperonyl butoxide <ul style="list-style-type: none"> • ULV fog • 0.002 to 0.0025 lbs/acre 	Ground (truck-mounted Leco sprayer)	Weekly. Time of spraying: 6pm - 7pm	Central America Research Station (CARS)	<i>An albimanus</i>
Malaysia (Seleena 2004)	Alphacypermethrin <ul style="list-style-type: none"> • 2 g AI/10⁴ x m² 	Ground, with hand-held sprayers	Monthly Time of spraying: not stated	Spray team of villagers, headed by a local public health inspector	(1°) <i>Anopheles balabacensis</i> (2°) <i>An sundaicus</i> , <i>An flavirostris</i>

Abbreviations: AI: active ingredient; ULV: ultra-low volume.

CONTRIBUTIONS OF AUTHORS

JP, LC, and DM developed the protocol.

JP and LC screened search outputs, selected trials for inclusion, extracted the data, and assessed risk of bias with support from DM as required.

MR conducted the modelling analysis and provided statistical support throughout.

JP, LC, and MR conducted the GRADE analysis.

JP prepared the draft manuscript, with contributions from all authors. All review authors have seen and approved the final manuscript.

DECLARATIONS OF INTEREST

JP has no known conflicts of interest.

LC has no known conflicts of interest.

MR has no known conflicts of interest.

During the completion of the review, DM was employed by the Innovative Vector Control Consortium (IVCC). The title of the review is related to the use of insecticide applications for malaria vector control. The IVCC as an organization has a programme of working with industry on the development of novel insecticides and other vector control tools. The IVCC has no current programmes specifically related to the development of space spray insecticides, but one project relates to their use in a malaria transmission setting. Since completing the review, DM has joined Sumitomo Chemicals, a manufacturer of vector control products.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The main difference between the review and the protocol is the clarification of the methods used for analysis of the ITS studies. Firstly, we did not anticipate that the studies would not tabulate outcome data, and we therefore needed to use a plot digitizer to extract this. Secondly, we were required to estimate numbers of the treated population by using census data for the treated villages, as these numbers were not reported for each study site. It also became apparent that the impact of space spraying on a time series of outcome data could be interpreted as both a step and a slope change. We therefore treated the step change and the slope change as different outcomes of the intervention, and we adopted the methodology from [Bernal 2017](#) to estimate the step rate ratio and slope rate ratio. Finally, we calculated both the step change in malaria incidence and the effect of the slope change after 12 months of space spraying, and presented both findings in [Summary of findings for the main comparison](#).