Effectiveness of indoor residual spraying on malaria control: a systematic review and meta-analysis

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Abstract

Background: Indoor residual spraying (IRS) is one of the key interventions recommended by World Health Organization in preventing malaria infection. We aimed to conduct a systematic review and meta-analysis of global studies about the impact of IRS on malaria control.

Method: We searched PubMed, Web of Science, Embase, and Scopus for relevant studies published from database establishment to 31 December 2021. Random-effects models were used to perform meta-analysis and subgroup analysis to pool the odds ratio (OR) and 95% confidence interval (CI). Meta-regression was used to investigate potential factors of heterogeneity across studies.

Results: Thirty-eight articles including 81 reports and 1,174,970 individuals were included in the meta-analysis. IRS was associated with lower rates of malaria infection (OR = 0.35, 95% CI: 0.27–0.44). The significantly higher effectiveness was observed in IRS coverage ≥ 80% than in IRS coverage < 80%. Pyrethroids was identified to show the greatest performance in malaria control. In addition, higher effectiveness was associated with a lower gross domestic product as well as a higher coverage of IRS and bed net utilization.

Conclusions: IRS could induce a positive effect on malaria infection globally. The high IRS coverage and the use of pyrethroids are key measures to reduce malaria infection. More efforts should focus on increasing IRS coverage, developing more effective new insecticides against malaria, and using multiple interventions comprehensively to achieve malaria control goals.

Keywords: Indoor residual spraying, Malaria, Meta-analysis, Effectiveness evaluation
remains a major public health concern globally, especially in Africa, where the deaths caused by malaria accounted for about 95% of deaths globally [1].

In the past decades, numerous measures have been developed and implemented to prevent the malaria epidemic. Between 2000 and 2015, at least 663 million malaria cases were estimated to be averted by using malaria control interventions, vector control measures in particular [2]. Indoor residual spraying (IRS) is a key component in vector control of malaria, which has been used and showed the effectiveness in a variety of countries [3]. IRS works via spraying a long-lasting residual insecticide to internal and exterior surfaces of a house where malaria vectors might rest and be killed by the insecticide [4]. In the 1930s, IRS with pyrethrum succeed on malaria control in South Africa and India [5]. Between the 1940s and the 1960s, several pilot projects performed in African countries aimed at eliminating malaria demonstrated that malaria could be highly responsive to control by IRS with insecticides. In addition, the goal of eliminating malaria has been achieved in the United States and some European countries by using IRS insecticides such as dichloro-diphenyl-trichloroethane (DDT) [6]. On 30 June 2021, China was certified by the World Health Organization (WHO) as a malaria-free country with 4 consecutive years of reporting no indigenous cases [7].

In recent years, most studies in African countries indicated that IRS was associated with reductions in the incidence of malaria [8–12]. For example, after three rounds of IRS with bendiocarb from December 2014 to December 2015 in Tororo, Uganda, the significantly lower incidence of malaria and prevalence of parasitemia were observed in the following investigations [8]. Another study in Uganda also showed the same association between IRS implementation and a lower incidence of malaria, though a waned reduction effect in malaria occurred 4 months following IRS [9]. However, the effectiveness of IRS was not consistent across studies. A study carried out in northern Zambia reported that IRS with pirimiphos-methyl contributed to 25% of decline in parasite prevalence during rainy seasons, while no such decline existed in dry seasons [13].

Although IRS might be a useful measure to control malaria, its coverage remains extremely low in malaria-endemic countries. According to the WHO report, the percentage of the population susceptible to malaria protected by IRS at the globe declined from 5.8% in 2010 to 2.6% in 2020 [1]. Low IRS coverage might have unfavorable effects on the progress towards global eradication of malaria. Thus, we need to pool existing evidence on the effectiveness of IRS to prevent malaria so as to inform intervention decisions and practices in malaria control. A previous systematic review and meta-analysis published in 2012 included 13 studies and indicated a summary risk reduction of 62% for malaria following the implementation of IRS [14]. In light of the limited number of original studies pooled and the lack of subgroup analysis in the previous meta-analysis, it is imperative to perform an updated one to provide more robust and comprehensive information by incorporating over 20 recent extra published literature and carrying out more in-depth and detailed analysis. In this study, we aimed to estimate the effect of IRS on malaria control based on all the related studies and analyze potential impact factors of IRS's effectiveness.

Methods
This systematic review and meta-analysis were conducted following the principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15].

Literature retrieval and selection criteria
We searched systematically for relevant studies published from database establishment to 31 December 2021 from PubMed, Web of Science, Embase, and Scopus. The searching strategy consisted of a combination of keyword items in titles or abstracts as follows: Malaria AND (Indoor residual spraying OR IRS OR Indoor residual spray) AND (effectiveness OR protection OR prevalence OR incidence OR rate OR ratio OR proportion). These keywords relevant to the study aims were determined according to the discussion among the authors and the retrieval strategies used in previous systematic reviews on malaria and epidemiological outcomes [14, 16]. In addition, reference lists of original studies included were checked for potential missed studies in database searches. We did not contact any authors for providing additional original data.

All studies obtained through the initial search were entered into EndNote version X9 (Clarivate, Philadelphia, Pennsylvania) to remove duplicates automatically. Two researchers YZ and MX independently carried out the screening of titles and abstracts, followed by a full-text check for remaining papers. Discrepancy in screening results was resolved by discussion in the two researchers and a consultation with another experienced researcher. Studies were selected for data extraction and subsequent data analysis if they met criteria concurrently as follows: (1) malaria was the target disease; (2) IRS was the only intervention measure; (3) authors reported the detailed number of cases and number of total population in the intervention group and the control group, or these values could be recalculated based on existing data in results; (4) the impact of IRS on malaria was assessed through before-after self-control or setting up another
control group without IRS implementation; (5) published in English. Eligibility of original studies was also assessed in accordance with several exclusion criteria as follows: (1) being a review, conference abstract, comment, or case report; (2) only reporting outcomes of entomological indicators; (3) reporting results from mathematical modelling other than data in the real world; (4) without estimating the impact of IRS on malaria or related indicators. In addition, when multiple studies reported results from the same resource population, studies with smaller sample sizes or shorter follow-up periods were excluded.

**Quality assessment and data extraction**

Quality assessment of original studies successfully passing the full-text screening was done using the Joanna Briggs Institute (JBI) Critical Appraisal tools checklist for analytical cross-sectional studies and checklist for quasi-experimental studies [17]. The two appraisal tools respectively included 9 and 10 items associated with study design and quality control. Studies with more than 50% of items met were regarded as eligible for further data analysis [18]. YZ and WZ independently carried out the quality assessment, and disagreement was addressed through discussion.

Data were extracted independently by YZ and MX with a predefined and standardized form, including study variables when available as follows: first author, publication year, study design, type of control (a before-after self-control or a blank control), study location, study population, malaria epidemic level, outcome indicator, malaria diagnosis method, type of IRS insecticide, frequency of IRS, IRS coverage, coverage of bed net, time of IRS implementation, time of IRS effectiveness evaluation, effect size [odds ratio (OR), risk ratio (RR), incidence rate ratio (IRR), and rate difference (RD)] indicating IRS impact and its 95% confidence interval (CI), and the number of cases and the number of total population in both intervention group and control group. Multiple records were extracted when there were multiple reports of targeted outcomes involving different investigation time points and locations. In addition, we accessed and documented the gross domestic product (GDP) in 2019 from Trading Economics website [19] and malaria incidence rate in 2019 from the website of WHO of the countries involved in original studies in this review to perform subgroup analyses.

**Statistical analysis**

The pooled OR and RR with 95% CI were used to evaluate the association between IRS and malaria risk. Cochran’s Q and $I^2$ statistics were used to estimate the heterogeneity among the studies [20]. $I^2 < 25\%$ and $I^2$ of 25–75% respectively denoted low heterogeneity and moderate heterogeneity, and $I^2 > 75\%$ was regarded as high heterogeneity. A random-effects model with Mantel–Haenszel method was used to do all the meta-analyses in light of high heterogeneity appeared across studies. Results were visualized through mapping forest plots. Some variables were used for subgroup analysis in light of heterogeneity, including study design, GDP in corresponding country (< 30 billion USD, 30–60 billion USD and ≥ 60 billion USD), incidence rate per 1000 population at risk (< 250 per 1000 and ≥ 250 per 1000), malaria epidemic level, IRS coverage (< 80% and ≥ 80%), bed net coverage (0%, 0–50%, 50–90%, ≥ 90% and unknown), and IRS chemicals. Subgroup analysis was only performed on datasets containing at least two studies. Meta-regression model was performed to compare the effects of IRS on malaria among different study-level variables. Sensitivity analysis was performed to strengthen reliability of the result by carrying out meta-analyses omitting each study to examine whether there was a study with disproportionately excessive impact. In addition, only the cross-sectional/case-control studies and only the cohort/randomized controlled trial (RCT) studies were kept to respectively calculate a pooled OR and RR in order to evaluate the stability of results. Funnel plot and Egger’s test were used to assess the potential bias of publication. $P < 0.05$ (two-sided) was defined as statistically significant. All data analyses were performed using Stata 17.0 (Stata Corp LP, College Station, TX, USA).

**Results**

**Overview of the included studies**

Among the 4268 records initially searched in electronic databases, 2463 duplicates in EndNote software, 1753 reports in screening of titles and abstracts, and 14 reports in screening of full texts, were removed. A total of 38 articles (81 reports) were included in the final analysis, composed of 25 cross-sectional studies, six cohort studies, five case-control studies, and two RCT studies (Fig. 1).

Results of quality assessment showed 36 observational studies fulfilled at least 5 items (5/8, 62.5%) of all items and they were all included. Two RCT studies fulfilled at least 8 items (8/9, 88.9%) and were also included (Additional file 1: Tables S1 and S2). The funnel plot presented symmetrical distribution of all studies, and the Egger’s test did not show any statistical significance ($P = 0.221$). Therefore, a low risk of publication bias was observed across studies in this systematic review (Fig. 2).

Of the 38 original articles included, 35 were carried out in African countries and only three were in India (Table 1). Twenty-eight were published after the year of 2010, and 19 focused on children. Rapid diagnostic test ($n = 23$) was the most frequent method used to diagnose malaria, followed by blood smear test ($n = 13$) and
clinical judgement \((n=2)\). Pyrethroids \((n=13)\) were the most common IRS insecticide used in articles, followed by the use of multiple insecticides \((n=12)\) and DDT \((n=4)\). In addition, 19 articles reported an IRS coverage at least 80%, 7 reported an IRS coverage less than 80%, and 12 did not report the value.

**Overall effect of IRS on malaria prevention**

This meta-analysis of 81 reports from 38 relevant articles [8, 10–13, 21–53] included a pooled study population that contained 1,174,970 individuals, with 801,953 individuals accepting IRS and 373,017 living without IRS. The combined \(OR\) based on a random-effects model for the association between IRS and the risk of malaria was estimated as 0.35 (95% CI: 0.27–0.44, \(I^2=100\%\)) (Fig. 3). Of the 81 reports, only 17 showed a crude odds ratio with upper limits of 95% CI passing one, denoting an unrelated or positive relationship between IRS and the risk of malaria. Most studies showed a protective effect for IRS on the risk of malaria.

**Subgroup meta-analysis on the effect of IRS on malaria prevention**

When classified by study design, 29 cohort reports and 45 cross-sectional reports showed a positive protection of IRS, with pooled \(OR\)s of 0.24 (95% CI: 0.16–0.36) and 0.44 (95% CI: 0.33–0.58), respectively. Five case-control reports and two RCT reports did not present statistically significant effectiveness of IRS on malaria (Fig. 4 and Additional file 1: Fig. S1).

When classified by the country’s GDP in 2019, studies in countries with a GDP < 30 billion dollars showed the best effectiveness of IRS (pooled \(OR=0.28\), 95% CI: 0.15–0.50), followed by that in countries with a GDP of 30–60 billion dollars (pooled \(OR=0.36\), 95% CI: 0.26–0.50) and a GDP ≥ 60 billion dollars (pooled \(OR=0.38\), 95% CI: 0.25–0.58), respectively (Fig. 4 and Additional file 1: Fig. S2).

When classified by malaria incidence rate in 2019, the highest effectiveness of IRS was observed in countries with malaria incidence rate < 250 per 1000 population at risk, while countries with rate ≥ 250 per 1000 population at risk performed slightly worse, with similar pooled \(OR\)s being 0.30 (95% CI: 0.19–0.45) and 0.40 (95% CI: 0.30–0.52), respectively. Similar differences also occurred in settings with different levels of malaria epidemic. Better protective effects of IRS were observed in studies reporting a low epidemic level compared to areas with a high level (pooled \(OR: 0.20\) vs 0.35) in Fig. 4 and Additional file 1: Fig. S3.

When classified by IRS insecticide, except for propoxur and pirimiphos methyl (both only with 3 reports), the other insecticides involved in studies showed significant
Table 1  Characteristics of original studies and the study populations

| First author | Publication year | Study design | Study country | Study location | Population | Malaria epidemic level | Outcome | Diagnosis method | IRS drug | IRS coverage |
|--------------|------------------|--------------|---------------|----------------|------------|------------------------|---------|------------------|----------|--------------|
| Jambou       | 2001             | Cross-sectional | Madagascar    | 168 municipalities | Children (mean 8.4 years) | High | Malaria parasites prevalence | Blood smear test | DDT | Unknown |
| Guyatt       | 2002             | Cross-sectional | Kenya         | Gucha District | General population | High | Plasmodium falciparum infection | RDT | Pyrethroids | Unknown |
| Gunasekaran  | 2005             | Cross-sectional | India         | Intervention: 54 villages; Control: 10 villages | General population | High | Plasmodium falciparum infection | Blood smear test | DDT | ≥ 80% |
| Sintasath    | 2005             | Cross-sectional | Eritrea       | 2779 households (12,937 individuals) from 5 zobas | General residents (except children aged < 1 month) | Low | Plasmodium falciparum and Plasmodium vivax infection | RDT | Multiple | Unknown |
| Singh        | 2006             | Cross-sectional | India         | 40 villages | Children ≤ 10 years; > 10 years | High | Malaria | RDT, blood smear test | Pyrethroids | ≥ 80% |
| Kleinschmidt | 2006             | Cross-sectional | Equatorial Guinea | 15 sentinel sites | 2–15 years | High | Plasmodium falciparum infection | RDT, blood smear test | Multiple | ≥ 80% |
| Protopopoff  | 2008             | Cross-sectional | Burundi       | 4 zones | 1–9 years, > 9 years | High | Malaria infection, high-density parasitemia, clinical malaria | Blood smear test, RDT | Multiple | ≥ 80% |
| Tseng        | 2008             | Cohort         | South Sudan   | All districts | Children aged < 9 years | High | Malaria parasitemia | Blood smear test | Pyrethroids | ≥ 80% |
| Bukirwa      | 2009             | Cross-sectional | Uganda        | Karungu District | General population | Medium | Clinical malaria | Microscopy | Pyrethroids | ≥ 80% |
| Zhou         | 2010             | Cohort         | Kenya         | 1100 houses | Children aged < 14 years | High | Malaria incidence, Plasmodium parasite infection, Plasmodium parasite prevalence | Blood smear test, RDT, blood smear test | Pyrethroids | ≥ 80% |
| Rehman       | 2011             | Cross-sectional | Malawi        | 14 sentinel sites | <15 years | High | Malaria | RDT, blood smear test | Pyrethroids | < 80% |
| Rehman       | 2011             | Cross-sectional | Mainland Equatorial Guinea | 2 provinces | <15 years | High | Malaria | RDT, blood smear test | Multiple | < 80% |
| Aregeawi     | 2011             | Cross-sectional | Zanzibar      | 6 inpatients facilities out of 7 in Zanzibar | General population | High | Malaria | Clinical judgement | Pyrethroids | ≥ 80% |
| Hamusse      | 2011             | Cross-sectional | Ethiopia      | 22 sprayed and 22 unsprayed villages | General population | High | Malaria incidence | Blood smear test | DDT | ≥ 80% |
| Skarbinski   | 2012             | Cross-sectional | Malawi        | 1 district (Nkhotakota District) | Children aged < 5 years | High | Malaria parasitemia | Blood smear test | Pyrethroids | ≥ 80% |
| First author | Publication year | Study design       | Study country     | Study location | Population | Malaria epidemic level | Outcome | Diagnosis method                  | IRS drug | IRS coverage |
|--------------|------------------|-------------------|------------------|----------------|------------|------------------------|---------|-------------------------------|----------|--------------|
| Fullman      | 2013             | Cross-sectional   | 17 countries in sub-Saharan Africa | NA            | Children aged < 5 years | High       | Parasitemia            | RDT and/or blood smear test | Multiple | Unknown       |
| Steinhardt   | 2013             | Cross-sectional   | Uganda           | 3 districts    | 0–59 months | High       | Parasite prevalence    | RDT      | Multiple                  | ≥ 80%    |              |
| Mashauri     | 2013             | Cross-sectional   | Tanzania         | 6 villages     | Children aged < 5 years | High       | Malaria parasitemia     | Blood smear test | Multiple | Unknown       |
| Mashauri     | 2013             | Cross-sectional   | Tanzania         | 6 villages     | Children aged 5–14 years | High       | Malaria parasitemia     | Blood smear test | Multiple | Unknown       |
| Mashauri     | 2013             | Cross-sectional   | Tanzania         | 6 villages     | Children aged ≥ 15 years | High       | Malaria parasitemia     | Blood smear test | Multiple | Unknown       |
| West         | 2013             | Cross-sectional   | Tanzania         | 68 villages    | Children aged 0.5–14 years | Medium     | Plasmodium falciparum infection | RDT      | Pyrethroids  | ≥ 80%    |
| Gimnig       | 2016             | Cross-sectional   | Kenya            | 2 districts    | General population | High       | Clinical malaria        | Parasitemia with fever | Pyrethroids | < 80%         |
| Hamainza     | 2016             | Cross-sectional   | Zambia           | 165 households in districts of Luangwa and Nymba | General population | High       | Malaria                 | RDT      | Multiple     | < 80%    |
| Kesteman     | 2016             | Case-control      | Madagascar       | 31 sentinel health centres | General population | High       | Clinical malaria        | RDT or microscopy | Pyrethroids | < 80%         |
| Odugbemi     | 2016             | Cross-sectional   | Nigeria          | 20 local government areas | < 5 years | High       | Parasitemia             | RDT      | Pyrethroids  | ≥ 80%    |
| Kesteman     | 2016             | Cross-sectional   | Madagascar       | 4 southern study sites | Children aged 0.5–14 years | Low       | Plasmodium infection    | RDT      | Pyrethroids  | Unknown  |
| Kesteman     | 2016             | Cross-sectional   | Madagascar       | 21 of all targeted zones except the south | Children aged 0.5–14 years | Low       | Plasmodium infection    | RDT      | Pyrethroids  | Unknown  |
| Wanzira      | 2017             | Cross-sectional   | Uganda           | 210 areas      | Children aged < 5 years | High       | Malaria parasitemia     | Blood smear test | Methylcarbamate | Unknown  |
| Raouf        | 2017             | Cross-sectional   | Uganda           | City (Apac District) | < 14 years | High       | Malaria                 | Microscopy or RDT | Multiple     | ≥ 80%    |
| Rek          | 2018             | Cohort            | Uganda           | Subcounty      | 0.5–11 years | High       | Parasite prevalence, malaria incidence | Blood smear test | Methylcarbamate | Unknown  |
| Hast         | 2019             | Cross-sectional   | Zambia           | Nchelenge District | General population | High       | Plasmodium falciparum  | RDT      | Multiple     | ≥ 80%    |
| First author | Publication year | Study design | Study country | Study location | Population | Malaria epidemic level | Outcome | Diagnosis method | IRS drug | IRS coverage |
|--------------|------------------|--------------|---------------|----------------|------------|----------------------|---------|------------------|----------|--------------|
| Nankabirwa   | 2019             | Cohort       | Uganda        | Subcounty      | 0.5–10 years and ≥ 18 years | High | Microscopic parasitemia | Blood smear test | Unknown | Unknown     |
| Loha         | 2019             | RCT          | Ethiopia      | 44 villages    | General residents | High | Malaria incidence, anemia | RDT | Methyl carbamate | ≥ 80%     |
| Tugume       | 2019             | Cohort       | Uganda        | 1 district     | ≥ 18 years | High | Malaria | RDT, blood smear test | Pirimiphos-methyl | ≥ 80%     |
| Arinaitwe    | 2020             | Case-control | Uganda        | 1 district     | General population with a history of recent overnight travel | Low | Malaria | RDT | Pirimiphos-methyl | Unknown |
| Habbarimana  | 2020             | Cross-sectional | Rwanda      | Village        | Children aged 6 months to 14 years | High | Malaria | RDT | Pyrethroids | < 80%     |
| Kamya        | 2020             | Cohort       | Uganda        | Tororo District | Children aged 6 months to 2 years | High | Parasitemia | Microscopy, PCR | Multiple | ≥ 80%     |
| Wubisheht    | 2021             | Case-control | The Republic of Nabimia | 1 district (Zambezi River region) | General population | High | Malaria | RDT | Methyl carbamate | ≥ 80%     |
| Smith        | 2021             | Case-control | The Republic of Nabimia | 1 district (Zambezi River region) | Residents aged < 76 years | High | Parasite, *Plasmodium falciparum* | RDT | DDT | < 80%     |
| Siegert      | 2021             | Case-control | India         | 1 district (Bangalore) | Residents aged > 18 years | Low | Plasmodium infection | PCR | Multiple | < 80%     |
| Chaccour     | 2021             | RCT          | Mozambique    | Rural Mopeia District | Children aged < 5 years | High | Malaria | RDT | Pirimiphos-methyl | Unknown |
| Fekadu       | 2021             | Cross-sectional | Ethiopia   | Health center | Patients in Heben Arsi District | Medium | Malaria | Blood smear test | Methyl carbamate | Unknown |

*RCT* randomized controlled trial, *RDT* rapid diagnostic test, *PCR* polymerase chain reaction, *DDT* dichloro-diphenyl-trichloroethane.
Fig. 3  The total effect of indoor residual spraying on the risk of malaria by the random effects model. $n_i$: the number of malaria cases who accepted indoor residual spraying (IRS); $N_i$: the number of people who accepted IRS; $n_c$: the number of malaria cases who did not accept IRS; $N_c$: the number of people who did not accept IRS; OR: odds ratio; CI: confidence interval.
Fig. 4 The effect of indoor residual spraying on the malaria control in subgroup analysis using the random effects model. $N_i$: the number of people who accepted indoor residual spraying (IRS); $N_c$: the number of people who did not accept IRS; OR: odds ratio; CI: confidence interval; $P$: $P$-value denoting the level of heterogeneity among studies; RCT: randomized controlled trial; DDT: dichloro-diphenyl-tricloroethane.
effects on the decrease of malaria incidence rate. Of these, pyrethroids had the lowest pooled OR of 0.29 (95% CI: 0.16–0.52), followed by DDT (OR=0.35, 95% CI: 0.16–0.78) and methyl carbamate (OR=0.36, 95% CI: 0.24–0.52) in Fig. 4 and Additional file 1: Fig. S4.

When classified by IRS coverage, it showed a stronger protective effect of IRS on the risk of malaria in the group with IRS coverage ≥ 80% with OR of 0.27 (95% CI: 0.17–0.43). In contrast, IRS coverage< 80% were not related to the decrease of malaria risk with OR of 0.53 (95% CI: 0.24–1.15). In addition, the effectiveness of IRS increased with the increase of the coverage of bed net in households. A significantly lower pooled OR (0.56 vs 0.35) was observed in the group of a coverage ≥ 90% (Fig. 4 and Additional file 1: Fig. S5).

**Results of meta-regression and sensitivity analysis**

In the multivariate meta-regression model including all the subgroup factors, none of these factors had any significant influence on effect sizes (all P>0.05) (Table 2). The results remained stable when conducting the leave-one-out sensitivity analysis (Additional file 1: Table S3). When only the 30 cross-sectional/case-control studies were kept, the overall pooled OR increased slightly from 0.35 (95% CI: 0.27–0.44) to 0.42 (95% CI: 0.31–0.56) (Additional file 1: Fig. S6). In the subgroup analysis within only cross-sectional/case-control studies, the most pooled estimates increased slightly. When only the eight cohort/RCT studies were kept, the pooled RR was 0.34 (95% CI: 0.23–0.49) (Additional file 1: Fig. S7). The effectiveness of IRS remained strong in most subgroup analysis.

**Discussion**

In this study, we pooled the results from 38 original articles (81 reports) regarding the effectiveness of IRS on the control of malaria, regardless of countries’ GDP, incidence rate of malaria, IRS coverage, type of IRS insecticide, epidemic level of malaria, coverage level of bed net, and study design among the studies included in analysis. Sensitivity analyses and results of funnel plot and the Egger’s test proved that no significant publication bias existed, and our findings were reliable and robust. High heterogeneity existed in the meta-analysis of overall studies and the subgroup analyses. However, all the variables in the subgroup analysis did not show a significant correlation with the outcome indicator.

A meta-analysis published in 2012 had the same research purpose as ours, which included only 13 original papers and concluded that IRS could reduce the risk of malaria by 62% [14]. This meta-analysis also found an excessive degree of heterogeneity across original studies and indicated a high initial prevalence of malaria, multiple spraying rounds, the use of DDT, and in areas with *Plasmodium falciparum* and *P. vivax* malaria were associated with better effectiveness of the implementation of IRS. Though there were some differences in spraying year, study design, and effect size used between this meta-analysis and ours, and more than 20 extra studies have been published since 2012, our study reported a reduced risk of 65% via performing IRS, which was very close to the value in the prementioned

Table 2 Multivariate meta-regression on the association between indoor residual spraying and malaria risk

| Variable                        | Coefficients (95% CI) | P-value |
|---------------------------------|-----------------------|---------|
| Study design                    |                       |         |
| Case-control study              | Reference             | –       |
| Cohort study                    | −0.607 (−2.344 to 1.130) | 0.493   |
| Cross-sectional study           | 0.323 (−1.179 to 1.825) | 0.673   |
| RCT study                       | 1.436 (−1.330 to 4.202) | 0.309   |
| GDP, billion dollars             |                       |         |
| < 30                            | Reference             | –       |
| 30–60                           | 0.863 (−0.920 to 2.646) | 0.343   |
| ≥ 60                            | 0.093 (−0.996 to 1.182) | 0.867   |
| Unknown                         | 0.843 (−1.925 to 3.611) | 0.551   |
| Incidence rate (/1000)           |                       |         |
| < 250                           | Reference             | –       |
| ≥ 250                           | 0.286 (−0.960 to 1.532) | 0.653   |
| IRS chemicals                   |                       |         |
| DDT                             | Reference             | –       |
| Pyrethroids                     | −0.010 (−1.374 to 1.354) | 0.989   |
| Methyl carbamate                | 0.070 (−2.034 to 2.173) | 0.948   |
| Pirimiphos-methyl               | −0.757 (−3.751 to 2.236) | 0.620   |
| Multiple                        | −0.099 (−1.529 to 1.332) | 0.893   |
| IRS coverage, %                 |                       |         |
| < 80                            | Reference             | –       |
| ≥ 80                            | 0.562 (−1.699 to 0.575) | 0.333   |
| Unknown                         | −0.059 (−1.546 to 1.428) | 0.938   |
| Net coverage, %                 |                       |         |
| 0                               | −0.286 (−2.461 to 1.890) | 0.797   |
| < 50                            | Reference             | –       |
| 50–90                           | −0.137 (−1.757 to 1.482) | 0.868   |
| ≥ 90                            | −0.908 (−3.282 to 1.467) | 0.454   |
| Unknown                         | −0.390 (−1.982 to 1.203) | 0.632   |
| Malaria epidemic level          |                       |         |
| High                            | Reference             | –       |
| Medium                          | −0.522 (−1.890 to 0.845) | 0.454   |
| Low                             | −0.793 (−2.104 to 0.517) | 0.235   |

CI confidence interval, RCT randomized controlled trial, GDP gross domestic product, DDT dichloro-diphenyl-tricloroethane, IRS indoor residual spraying
meta-analysis. Therefore, the effectiveness of IRS has obtained further confirmation.

We found the effectiveness of IRS on malaria decreased slightly with a higher GDP of countries. It may be explained by the fact that richer countries have been providing multiple and high-quality intervention measures against malaria to their citizens for a long term. In addition, people living in a more affluent and urbanized country usually enjoy better housing conditions with other effective measures to protect them from mosquito bites. Therefore, countries with a high GDP might use effective alternative interventions and mask the effectiveness of IRS. Zhao et al. found an increased per-capita GDP might indirectly influence the reduction of malaria cases at a macro level [54], and Xu et al. reported a negative correlation between annual malaria incidence and national GDP [55]. Countries with a relatively low GDP should allocate locally available IRS resources properly and simultaneously apply other effective interventions to contain the malaria epidemic. In the subgroup analysis, we also found a better protective impact of IRS in countries with a lower malaria incidence rate. Due to the subtle difference existing in OR values across studies with different malaria incidences, we cannot conclude that IRS's effectiveness was associated with malaria incidence.

Higher effect of IRS was found in countries and areas with IRS coverage ≥ 80%. In contrast, it was much less effective in settings with IRS coverage < 80%. This finding is consistent with some previous investigations. Elmardi et al. used a multilevel multivariate logistic regression model to analyze cross-sectional data, and demonstrated that a higher level of IRS coverage was associated with fewer malaria infections [56]. Another study showed a negative relationship between IRS coverage and malaria incidence but did not obtain a statistical significance [57]. It has been proved that stopping IRS in Uganda, a country with a high bed net coverage, would be faced with a fivefold increase in malaria incidence within 10 months [58]. As a result, IRS could play a critical role in achieving global malaria targets, and its coverage should be promoted as high as possible through improved community engagement [57]. Furthermore, this study upheld the WHO guidance on IRS coverage of at least 80% in order to have significant effectiveness and thereafter benefit the community.

In the subgroup analysis, DDT, pyrethroids, methyl carbamate, and combined use of multiple insecticides showed great effectiveness in controlling malaria, particularly pyrethroids. Pirimiphos-methyl did not present an obvious protective impact. Only three studies performed this IRS insecticide, therefore corresponding pooling estimates might not be accurate and reliable. This review included original reports carried out in a large time span, thus our results can only reflect the effectiveness of IRS insecticides in the past other than right now. An increased number of studies have reported the rapid spread of insecticide resistance in malaria vectors and rebounds of malaria in some endemic areas. Almost all of IRS insecticides reviewed in this study were reported to have generated or to be generating resistance among malaria vectors such as Anopheles culicifacies, An. gambiae, An. coluzzii, and An. stephensi in different countries and areas [59–64]. Therefore, the increasing resistance of IRS insecticides may pose a growing threat to malaria control, the monitoring of local insecticide resistance before implementation of IRS might be necessary to pick out an insecticide with a high sensitivity for local malaria vectors. In addition, IRS using alternative insecticide formulations may be needed.

We also observed better IRS effects in settings with a higher bed net coverage compared with settings without net. This is reasonable that comprehensive use of multiple intervention measures against malaria performs better than single use. A review published in 2009 drew a similar conclusion that combined use of IRS and nets was more protective relative to IRS alone (OR=0.71 and 0.63 in two studies, respectively) [65]. Gimnig et al. found IRS could provide added benefits in an area of moderate to high transmission with moderate ITN coverage, while the value of adding ITNs to IRS remained unclear as their benefits were likely to be masked by IRS [49]. A modeling study concluded that long-lasting insecticidal net use of 56% and IRS coverage of 70% was the most cost-effective malaria control strategy in western Kenya [66]. Based on above evidence, the necessity and potential benefits of performing IRS and improving IRS coverage are further highlighted. Research on how to maximize the benefits of using two measures concurrently, particularly in the context of increasing resistance to IRS insecticides, is encouraged [49].

Some limitations should be acknowledged in this systematic review and meta-analysis. First, most of original studies were cross-sectional studies, which could only provide limited epidemiological evidence. Second, malaria definition included multiple indicators such as parasites infection, Plasmodium falciparum infection, malaria parasitemia, clinical malaria symptoms, and microscopic parasitemia. Inconsistent diagnostic methods and criteria might influence the comparison within these studies. Third, periods from IRS implementation to outcome measuring varied among studies, thus the effect sizes might not be comparable across them and the accuracy of pooling estimates was impacted. Fourth, the vectors and their resistance were inconsistent among countries and areas, which might lead to the underestimation of IRS's effect. In addition, it seemed
some unreasonable to observe a higher effectiveness of IRS in areas with a lower malaria incidence and epidemiologic level in the results, though the differences were tiny. The association between IRS effectiveness and malaria might be distorted by some confounding factors across studies such as insecticide assistance and spraying frequency. This issue is worth further investigation with confounding factors controlled.

Conclusions
IRS showed a positive effect on the control of malaria globally. In the past decades of fighting against malaria, IRS played an essential role in killing of pathogen-carrying vectors and preventing people from infection with malaria. Effectiveness was associated with the IRS coverage and the type of IRS insecticide. Higher IRS coverage and the use of pyrethroids are key measures to reduce malaria infection, and other interventions can be supplemented in malaria prevention. However, growing insecticide resistance should be paid more attention to before the implementation of IRS. The policy makers should also consider factors concerning IRS implementation such as GDP, incidence and prevalence rate of malaria, and IRS coverage to direct the formulation of policies. More efforts should focus on increasing IRS coverage, developing more effective new insecticides against malaria and implementing multiple interventions comprehensively for specific settings in the future.

Abbreviations
IRS: Indoor residual spraying; OR: Odds ratio; DDT: Dichloro-diphenyl-trichloroethane; WHO: World Health Organization; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; JBI: Joanna Briggs Institute; RR: Relative ratio; IRR: Incidence rate ratio; RD: Rate difference; CI: Confidence interval; GDP: Gross domestic product; RCT: Randomized controlled trial.

Supplementary Information
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Additional file 1: Table S1. Quality assessment of observational studies. Table S2. Quality assessment of RCT studies. Table S3. Sensitivity analysis by omitting each article. Figure S1. The effect of IRS on the malaria incidence classified with confounding factors controlled. Figure S2. The effect of IRS on the malaria incidence classified by GDP using the random effects model. Figure S3. The effect of IRS on the malaria incidence classified by malaria incidence rate (A) and malaria epidemic level (B) using the random effects model. Figure S4. The effect of IRS on the malaria incidence classified by IRS insecticide using the random effects model. Figure S5. The effect of IRS on the malaria incidence classified by IRS insecticide using the random effects model. Figure S6. The effect of IRS on the malaria incidence in subgroup analysis using the random effects model only within cross-sectional/case-control studies. Figure S7. The effect of IRS on the malaria incidence in subgroup analysis using the random effects model only within cohort/RCT studies.

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Author contributions
YZ, W-XZ, and ET collected and analyzed the data, prepared figures and tables, authored drafts of the paper, and approved the final draft. M-ZX, S-SZ, X-RW, JD, XF, T-TW, Y-LZ and Y-QL searched and collected the data and approved the final draft. Q-BL, FC and XZ conceived and designed the study, reviewed drafts of the paper, and approved the final draft. All authors have agreed to the published version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its Additional files.

Declarations

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Competing interests
The authors declare that they have no competing interests.

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References
1. World Health Organization. World malaria report 2021. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021. Accessed 27 June 2022.
2. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on Plasmadium falciparum in Africa between 2000 and 2015. Nature. 2015;526(7572):207–11.
3. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004;2:CD000363.
4. World Health Organization. Use of indoor residual spraying for scaling up global malaria control and elimination. https://apps.who.int/iris/bitstream/handle/10665/69386/WHO_HTM_MAL_2006.1112_eng.pdf?sequence=1&isAllowed=y. Accessed 25 Mar 2022.
5. Russell TL, Beebe NW, Cooper KD, Lobo NF, Burkom TR. Successful malaria elimination strategies require interventions that target changing vector behaviours. Malar J. 2013;12:56.
6. Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. Cochrane Database Syst Rev. 2010;2010(4):CD006657.
7. Burki T. Triumph in China as it is certified malaria-free by WHO. Lancet Infect Dis. 2021;21(9):1220–1.
8. Nankabirwa JI, Briggs J, Rek J, Arinaitwe E, Nyakabira P, Katrak S, et al. Persistent parasitemia despite dramatic reduction in malaria incidence after 3 rounds of indoor residual spraying in Tororo, Uganda. J Infect Dis. 2019;219(7):1104–11.
9. Tukee BB, Reke A, Lamadred-Figueroa H. Assessing the effect of indoor residual spraying (IRS) on malaria morbidity in Northern Uganda: a before and after study. Malar J. 2017;16(1):4.
10. Fekadu A, Dobso B, Birmeke M. Prevalence of, and risk factors for, malaria infection among patients visiting Golgota Health Center, Heben Arsi District, West Arsi Zone, Oromia Regional State, Ethiopia: a retrospective and an institution-based cross-sectional study. Ethiop J Health Dev. 2021;35(1):50–7.
11. Chaccour C, Zulliger R, Wagman J, Casellas A, Nacima A, Elobolobo E, et al. Incremental impact on malaria incidence following indoor residual spraying in a highly endemic area with high standard ITN access in Mozambique: results from a cluster-randomized study. Malar J. 2021;20(1):184.
12. Kamya MR, Kakuru A, Muhindo M, Arinaitwe E, Nankabirwa JI, Rek J, et al. The impact of control interventions on malaria burden in young children in a historically high-transmission district of Uganda: a pooled analysis of cohort studies from 2007 to 2018. Am J Trop Med Hyg. 2020;103(2):785–92.
13. Hast MA, Chapenda M, Muleba M, Kabuya JB, Lupuya J, Kobayashi T, et al. The impact of 3 years of targeted indoor residual spraying with permiphos-methyl on malaria parasite prevalence in a high-transmission area of Northern Zambia. Am J Epidemiol. 2019;188(12):2120–30.
14. Kim D, Fedak K, Kramer R. Reduction of malaria prevalence by indoor residual spraying: a meta-regression analysis. Am J Trop Med Hyg. 2012;87(1):117–24.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews and meta-analyses. J Clin Epidemiol. 2021;134:178–89.
16. Chan K, Tueting LS, Bottomley C, Saito K, Djouaka R, Lines J, et al. The effect of socioeconomic factors and indoor residual spraying on malaria in Mangaluru, India: a case–control study. Int J Environ Res Public Health. 2021;18(22):11853.
17. Rek JC, Alegana V, Arinaitwe E, Cameron E, Kamya MR, Katureebe A, et al. Rapid improvements to rural Ugandan housing and their association with malaria from intense to reduced transmission: a cohort study. Lancet Planet Health. 2018;2(2):e83–94.
18. Teshome A, Adane A, Girma B, Yalnus M, Tadesse B, Yitayew Z, et al. Resurgence of malaria following discontinuation of indoor residual spraying of insecticide in an area of Uganda with previously high-transmission intensity. Clin Infect Dis. 2017;65(3):453–60.
19. Protopopoff N, Van Bortel W, Marcotty T, Van Herp M, Maes P, Baza D, et al. Spatial targeted vector control is able to reduce malaria prevalence in the highlands of Burundi. Am J Trop Med Hyg. 2008;79(1):12–8.
20. Odugbemi BA, Wright KO, Onajole AT, Kuyinu YA, Goodman OO, Odugbemi TO, et al. A malarialometric survey of under-fives residing in indoor residual spraying-implementing and non-implementing communities of Lagos, Nigeria. Malar J. 2016;15(1):458.
21. Masihauri FM, Krunghi SM, Kaatano GM, Magesa SM, Ishmael KM, Mwanga J, et al. Impact of indoor residual spraying of lambdacyhalothrin on malaria prevalence and anaemia in an epidemic-prone district of Muleba, north-western Tanzania. Am J Trop Med Hyg. 2013;88(5):841–9.
22. Loha E, Diasessa W, Gani T, Bakew M, Kenea S, Solomon T, et al. Long-lasting insecticidal nets and indoor residual spraying may not be sufficient to eliminate malaria in a low malaria incidence area: results from a cluster randomized controlled trial in Ethiopia. Malar J. 2019;18(1):111.
23. Kleinschmidt I, Sharp B, Benavente LE, Schwabe C, Torres M, Kukiuki J, et al. Reduction in infection with Plasmodium falciparum one year after the introduction of malaria control interventions on Bioko Island, Equatorial Guinea. Am J Trop Med Hyg. 2006;74(6):972–8.
24. Keateman T, Randriananavelovozoa M, Raharin ongoing malaria control interventions in Madagascar. Malar J. 2016;15:112.
25. Jambou R, Ranaivo L, Raharinomalala L, Randriananvelovozoa M, Piola P, Rogier C. Post-deployment effectiveness of malaria control interventions on Plasmodium infections in Madagascar: a comprehensive phase IV assessment. Malar J. 2016;15:322.
26. Harousseau S, Balcha TT, Belachev T. The impact of indoor residual spraying on malaria incidence in East Shoa Zone, Ethiopia. Glob Health Action. 2012;5:11619.
27. Hamaza B, Sikaela CH, Moonga HB, Chanda J, Chinula D, Mwenda M, et al. Incremental impact upon malaria transmission of supplementing pyrethroid-impregnated long-lasting insecticidal nets with indoor residual spraying using pyrethroids or the organophosphate, permiphos methyl. Malar J. 2016;15:100.
46. Habyarimana F, Ramroop S. Prevalence and risk factors associated with malaria among children aged six months to 14 years old in Rwanda: evidence from 2017 Rwanda malaria indicator survey. Int J Environ Res Public Health. 2020;17(21):7975.

47. Guyatt HL, Corlett SK, Robinson TP, Ochola SA, Snow RW. Malaria prevalence in highland Kenya: indoor residual house-spraying vs. insecticide-treated bednets. Trop Med Int Health. 2002;7(4):298–303.

48. Gunasekaran K, Sahu SS, Jambulingam P, Das PK. DDT indoor residual spray, still an effective tool to control Anopheles fluviatilis-transmitted Plasmodium falciparum malaria in India. Trop Med Int Health. 2005;10(2):160–8.

49. Grimig JE, Oteino P, Were V, Marwanga D, Abongo D, Wiegand R, et al. The effect of indoor residual spraying on the prevalence of malaria parasite infection, clinical malaria and anaemia in an area of perennial transmission and moderate coverage of insecticide treated nets in Western Kenya. PLoS One. 2016;11(1):e0145282.

50. Fullman N, Bursttein R, Lim SS, Medlin C, Gakidou E. Malaria mortality and child mortality in sub-Saharan Africa. Malar J. 2013;12:62.

51. Bukirwa H, Yau V, Kigozi R, Fillier S, Quick L, Lugemwa M, et al. Assessing the impact of indoor residual spraying on malaria morbidity using a sentinel site surveillance system in western Uganda. Am J Trop Med Hyg. 2009;81(4):611–4.

52. Arinaitwe E, Mpeibaza A, Nankibirwa JI, Kamya M, Asimwe A, Kuule JK, et al. Malaria diagnosed in an urban setting strongly associated with recent overnight travel: a case–control study from Kampala, Uganda. Am J Trop Med Hyg. 2020;103(4):1517–24.

53. Aregawi MW, Ali AS, Al-mafazy AW, Molteni F, Katikiti S, Warsame M, et al. Reductions in malaria and anaemia case and death burden at hospitals following scale-up of malaria control in Zanzibar, 1999–2008. Malar J. 2011;10:46.

54. Zhao X, Thanapongtharm W, Lawawirojwong S, Wei C, Tang Y, Zhou Y, et al. Spatiotemporal trends of malaria in relation to economic development and cross-border movement along the China-Myanmar Border in Yunnan Province. Korean J Parasitol. 2020;58(3):267–78.

55. Xu JW, Li JJ, Guo HP, Pu SW, Li SM, Wang RH, et al. Malaria from hyperendemicity to elimination in Hekou County on China-Vietnam border: an ecological study. Malar J. 2017;16(1):66.

56. Elmardi KA, Adam I, Malik EM, Kafy HT, Abidin MS, Kleinschmidt I, et al. Impact of malaria control interventions on malaria infection and anaemia in areas with irrigated schemes: a cross-sectional population-based study in Sudan. BMC Infect Dis. 2021;21(1):1248.

57. Mumbengewui DR, Sturrock H, Hisang M, Roberts K, Kleinschmidt I, Ngiphumwa M, et al. Is there a correlation between malaria incidence and IRS coverage in western Zambezi region, Namibia? Public Health Action. 2018;8(Suppl 1):S44–9.

58. Namuganga JF, Epstein A, Nankibirwa JI, Mpeibaza A, Kiggundu M, Ssevwanga A, et al. The impact of stopping and starting indoor residual spraying on malaria burden in Uganda. Nat Commun. 2021;12(1):2635.

59. Mishra AK, Bharti PK, Chand G, Das A, Jayswar H, Rahi M, et al. Monitoring of insecticide resistance in Anopheles culicifacies in twelve districts of Madhya Pradesh, Central India (2017–2019). J Trop Med. 2022;2022:4404027.

60. Rakotoson JD, Fornadel CM, Belemvire A, Norris LC, George K, Caranci A, et al. Insecticide resistance status of three malaria vectors, Anopheles gambiae (s.s.), An. funestus and An. maculatus, from the south, central and east coasts of Madagascar. Parasites Vectors. 2017;10(1):396.

61. Ibrahim SS, Mukhtar MM, Irving H, Labbo R, Kusimo MO, Mahamadou I, et al. High Plasmodium infection and multiple insecticide resistance in a major malaria vector Anopheles coluzzi from Sahel of Niger Republic. Malar J. 2019;18(1):181.

62. Soma DD, Zogo B, Hien DFS, Hien AS, Kaboët DA, Kientega M, et al. Insecticide resistance status of malaria vectors Anopheles gambiae (s.s.) of southwest Burkina Faso and residual efficacy of indoor residual spraying with microencapsulated pirimiphos-methyl insecticide. Parasites Vectors. 2021;14(1):58.

63. Thiaw O, Doucoure S, Soucoufara S, Bouganali C, Konaté L, Diagne N, et al. Investigating insecticide resistance and knock-down resistance (kdr) mutation in Dielmo, Senegal, an area under long lasting insecticide-treated nets universal coverage for 10 years. Malar J. 2018;17(1):123.

64. Orjuela LL, Morales JA, Ahumada ML, Rios JF, González JJ, Yañez J, et al. Insecticide resistance and its intensity in populations of malaria vectors in Colombia. Biomed Res Int. 2018;2018:9163543.

65. Kleinschmidt I, Schwabe C, Shiva M, Segura JL, Sima V, Mabunda SJ, et al. Combining indoor residual spraying and insecticide-treated net interventions. Am J Trop Med Hyg. 2009;81(3):519–24.

66. Stuckey EM, Stevenson J, Galactionova K, Badjoa AY, Bousema T, Odongo W, et al. Modeling the cost effectiveness of malaria control interventions in the highlands of western Kenya. PLoS One. 2014;9(10):e107700.