The Effect of Combining Insecticide Treated Nets and Indoor Residual Spraying for Vector Control of Malaria: A Systematic Review

by

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Throughout a large portion of our planet, malaria has been nearly eradicated or reduced to levels that are highly manageable, and many countries possess the means to effectively treat the disease. However, many areas of the world, such as Sub-Saharan Africa and Southeast Asia, are still heavily burdened by malaria. In order to manage the transmission of malaria and reduce its prevalence throughout these areas of the world, the World Health Organization recommends implementation of vector control. Insecticide treated nets and indoor residual spraying are among the most effective methods for controlling the malaria vector. However, it is undetermined whether combining both of these treatments allows for an additional benefit to controlling the vector and reducing the transmission of malaria. Several studies published within the past five years have investigated the presence of an added benefit by combining these treatments within areas of Sub-Saharan Africa. In this thesis, a systematic review was performed in order to identify relevant studies. Full text analysis was then implemented in order to abstract meaningful data from these studies. Compared to past reviews, this review identified a higher degree of support for the presence of an added benefit when both treatments are combined. Recommendations for future studies on the subject matter were provided in order to promote the reduction of malaria prevalence throughout affected regions of the world.

Bachelor of Arts in International Studies in Bioengineering thesis of Jonathan Pak Kin Feng presented on June 5, 2017.

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Background

History

Extensive documentation throughout the different ages of human history allude to the fact that malaria is disease that has been commonly known of since the existence of humanity. However, the malaria protozoa likely originated over 30 million years ago, during the Palaeogene Period.[1] Because the protozoan is highly dependent on transmission via its hosts to survive, evolutionary biologists believe that it evolved alongside mosquitoes and non-human primates.[2] Geographically, it is likely that the parasite originated in Africa, as polymerase chain reaction (PCR) techniques suggest a high prevalence of *Plasmodium falciparum* malaria in ancient Egypt. Throughout human history, the disease has been noted among various civilizations. As early as 2700 BC, the symptoms of the disease had been documented in Chinese medical writings. Being a disease that plagued many Greek city-states, the symptoms of malaria were also documented by the Greek physician Hippocrates as early as 400 BC.[3]

During the second century BCE, the first notable treatments for malaria were discovered by the Chinese. They noted that treatment with the Qinghao plant allowed for reduction in the fevers of infected individuals. Spanish missionaries during the 17th century were also taught about the antimalarial properties of the Cinchona tree by the indigenous populations of South America.[3] However, it was not until 1880 that the parasite associated with malaria would be discovered. Charles Louis Alphonse Laveran, a French army physician, reported the presence of a protozoan parasite in the blood of soldiers suffering from malaria. Since this discovery, various antimalarial treatments and vector control methods have been created. Nevertheless, the disease continues to

burden many countries throughout the developing world.[3]

Public Health Impact

Since the beginning of the 21st century, the World Health Organization (WHO) has monitored the epidemiology of malaria as part of its Millennium Development Goals. One optimistic fact that has been gathered from this initiative is that between 2010 and 2015, there was a 14% decrease in the number of reported malaria cases worldwide.[4] This reduction has been associated with a 22% decrease in the total number of deaths due to malaria.[4] Despite these improvements, however, many countries continue to suffer from disproportionately high rates of malaria, particularly countries within the region of Sub-Saharan Africa. According to the WHO 2016 Malaria Report, 13 countries accounted for approximately 75% of the total number of deaths due to malaria.[5] Twelve of these countries are located within the continent of Africa. Within Africa, the countries that are most heavily affected are Nigeria (mortality rate of 4 deaths per 100,000), the Democratic Republic of the Congo (50 deaths per 100,000), and Mali (9 deaths per 100,000).[3] After Africa, the region that is most heavily burdened by malaria is Southeast Asia. This region alone accounts for 7% of all deaths attributed to malaria.[4,5]

Classical presentation of malaria typically involve a recurrence of chill and shivering followed by a fever and sweating. These symptoms will repeat in a cycle that ranges from two to three days, depending on the strain of infection. Other symptoms include headache, vomiting, hematuria (blood in the urine), jaundice, joint pain, and convulsions.[6] The most severe form of malaria is typically caused by *Plasmodium Falciparum*, as infection with this particular vector is

accompanied by neurological symptoms, such as seizures, nystagmus, abnormal posturing, and coma.[6]

Epidemiology

From a geographical perspective, resistant malaria has most heavily occurred in Sub-Saharan Africa, Southeast Asia, and the northern areas of South America, such as Brazil, Peru, Venezuela, and Colombia. These cases most frequently occur in children under the age of 15 and pregnant women. In 2015 alone, 214 million new cases of malaria were reported worldwide.[4] However, it is also important to note that this figure merely account for diagnosed cases, and that many occurring cases likely go undiagnosed. Again, the continent of Africa is by far the region most affected by malaria, as its population accounts for 90% of the new cases.[4] Ghana reported the highest incidence rate (26.1%), followed by the Democratic Republic of the Congo (23.8%) and Uganda (21.1%).[7] In Southeast Asia, the countries most heavily burdened by the disease consist of India (incidence rate of 1%), Indonesia (0.5%), and Myanmar (0.4%).[7]

The disease is still a major target of the WHO's initiatives, and they report that since their MGD of "…reversing the incidence of malaria," the attributed deaths to malaria has decreased by 60% between 2000 and 2015.[8] Furthermore, the 2016 World Malaria Report states that "…the incidence rate of malaria is estimated to have decreased by 41% globally between 2000 and 2015, and by 21% between 2010 and 2015."[8]

Malaria Vector and Parasites

The most notable malarial parasites are *Plasmodium Vivax, Plasmodium Ovale,* and *Plasmodium Falciparum*. Each of these organisms manifest themselves in malaria through different mechanisms and characteristics, however, they are all transmitted in mosquito bites when the saliva makes contact with the bloodstream. Specifically, the malaria parasite is transmitted through female mosquitoes of the genus *Anopheles*.[9] The life cycle of the malaria parasite involves the utilization of two hosts. The cycle begins with an initial injection of sporozoites by a female *Anopheles* mosquito into human host. Upon injection, the malaria sporozoites travel to the liver in the human body via blood vessels. There, the spores proliferate within hepatocytes (liver cells) and remain dormant for a period than can range from 8–30 days.[9] During this dormant period, the sporozoites mature into schizonts and escape from their infected hepatocytes, inducing cell lysis and releasing merozoites. Interestingly, the parasites *Plasmodium Vivax* and *Plasmodium Ovale* are able to remain in the liver even after inducing cell lysis. This allows the parasite to cause malarial relapses that can occur weeks after the initial infection.[10]

Upon being released from the liver, the merozoites target erythrocytes (red blood cells) and undergo asexual reproduction. The progeny of this reproduction are referred to as trophozoites. Within the erythrocytes, the trophozoites mature into schizonts and induce cell lysis once again. At this point, the released merozoites can undergo differentiation and mature into gametocytes. Differentiation into gametocytes marks a key point in the life cycle of these parasites, as the presence of gametocytes allows for further infection of additional human hosts. Mosquitoes that bite the infected human host ingest these gametocytes, and the mosquito body allows for the formation of sporozoites.[11] The sporozoites then travel to the salivary glands of the mosquito,

and are now ready to infect another human host. (CDC) This life cycle is depicted below in Figure 1.

Interventions

Treatment for a malaria infection is typically dependent on the severity of the patient's symptoms. Rapid treatment is prioritized, as the disease can rapidly increase in severity during the time between detection and treatment. Administering fluids and having the patient rest is crucial for treatment of the malaria-associated fevers. For uncomplicated malaria, the WHO highly recommends the use of artemisinin-based combination therapies (ACTs). ACTs use artemisinin derivatives along with a "partner drug" in order to reduce the amount of parasites

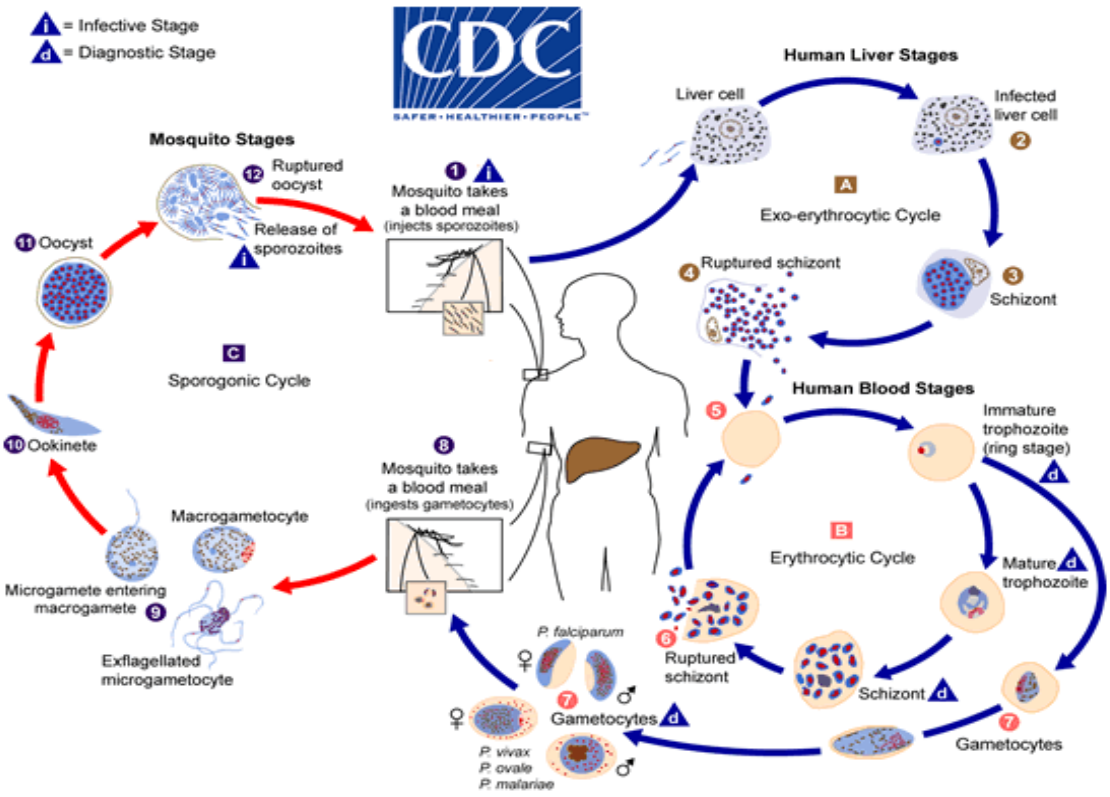

Figure 1 – Illustration of the life cycle of the malarial parasites, *Plasmodium Vivax, Plasmodium Ovale,* and *Plasmodium Falciparum*. The exo-erythrocytic and erythrocytic cycles, outlined in blue, take place within the human host. The sporogonic cycle, outlined in red, takes place within a female *Anopheles* mosquito and allows for the generation of additional sporozoites.[11] Taken from https://www.cdc.gov/malaria/about/biology/.

within the bloodstream of the patient. Artemisinin derivatives directly target the mitochondria of the parasites, which induces parasite death.[12] For treatment of severe malaria, patients are typically administered intravenous or intramuscular artesunate over the course of 24 hours. This is then followed by a three-day course of ACTs. These treatments are regarded as effective for the management of malaria, although access to ACTs remains poor in some of the most heavily burdened countries.[12]

In order to properly allocate medical resources for individuals affected by malaria, medical professionals utilize diagnostic testing to identify the portion of the population that is burdened by the disease. These appear as either microscopy tests or rapid diagnostic tests (RDTs). According to the World Health Organization, there are approximately 200 different types of RDT products on the market.[13] However, the majority of these products utilize the same method to test for malaria, which is typically the finger-prick method. Malaria transmission is associated with the presence of specific antigens, and RDTs measure the presence of these antigens in the blood of the tested individual. Results are typically returned within 15-30 minutes of starting the diagnostic test.[13]

Pregnant women are particularly susceptible to malaria, and therefore it is recommended that they receive intermittent preventative treatment (IPTp). Specifically, the WHO states that in areas where the population is at-risk for malaria, pregnant women should receive an IPTp dose at every antenatal care (ANC) visit following their first trimester.[13] As part of their initiative, the World Health Organization has attempted to make IPTp's more accessible to pregnant women.

From their efforts, they report that "…The proportion of pregnant women receiving at least one dose of IPTp has increased in recent years, but was still only 52% in 2014."[13]

Finally, malaria is also controlled by limiting the transmission of malaria through mosquitoes. These techniques are known as vector control. The main methods of vector control are insecticide treated nets (ITNs) and indoor residual spraying (IRS).[14] ITNs are typically used in the context of a bed net, where the user attaches the corners of the net to the ground or under the mattress and allows the net to hang above the bed. With regards to reducing malaria transmission, ITNs are thought to be twice as effective as nets without insecticides and offer approximately 70% more protection than not using any nets at all. Because of their proximity to the user, the chemicals used in ITNs are usually pyrethroids, which have a low toxicity relative to other insecticides.[14]

Various insecticides can be used in the application of IRS. Based on data regarding their efficacy and toxicity, the WHO has determined DDT, cyfluthrin, and deltamethrin. Cyfluthrin and deltamethrin are pyrethroids, which are similar to the chemicals used in ITNs.[14] Therefore, the toxicity of these insecticides are not a large concern. DDT, however, must be closely monitored so that it is not overused. Furthermore, DDT is only utilized in the context of public health operations, since its agricultural uses are not allowed under the Stockholm Convention.[15]

Previous Reviews and Potential for Further Investigation

There have been major reductions in the incidence and prevalence of malaria since the World Health Organization began its initiative in 2000. These reductions have been associated with a

high increase in vector control methods, especially in the region of sub-Saharan Africa. In between 2000 and 2012, the proportion of the population utilizing ITNs in sub-Saharan Africa increased by 34%.[16] Additionally, the proportion of the population in this region that was protected by IRS increased "…from 5% in 2005 to 11% in 2011, but fell to 8% in 2012."[16] The impact of these results is tremendous, although the WHO is continuing to further reduce the transmission of malaria. In order to increase the rate of malaria reduction, many governments have attempted to combine ITNs and IRS. However, there is no clear data to suggest that combination of these two vector control methods offers any additional benefit than utilizing one treatment. This systematic review serves to draw conclusions on the efficacy of combining ITNs and IRS by analyzing studies already performed within sub-Saharan Africa.

In 2014, the WHO performed an analysis of studies that investigated the effect of combining ITNs and IRS. This study examined both observational and randomized trials performed in Benin, Sudan, Tanzania, Gambia, Equatorial Guinea, Kenya, and Burundi. This review concluded that it was "…not possible to draw firm conclusions on whether the combination is generally beneficial in comparison to providing a single intervention."[16] However, it is important to recognize that this review was not systematic and therefore may have not detected articles that could have been viable for review.

Another review was done in 2011 by a group that had previously carried out studies in Tanzania on the combination of ITNs ad IRS. In this review, the authors proposed that any added benefit from combining ITNs and IRS would be dependent on the specific chemicals that used in each treatment. They suggested that "…highly deterrent IRS compounds coupled with highly toxic

ITNs" would be more effective at vector control than using both treatments with similar insecticides.[17] They also state that the observed effects of combining these treatments is modified by behavior of the malaria vector as well as proportion of the population that receives combined treatments. This review concluded by asserting that further investigations alongside mathematical modeling need to be done in order to further evaluate the effects of combining ITNs and IRS.

Since the most recent review in 2014, several additional studies on combining vector control methods have been performed within the region of Sub-Saharan Africa. The availability of these additional sources of data may allow for more trends to be identified in the efficacy of combining vector control methods. At this point in time, it is of upmost importance to determine what benefits – if any – exist. Understanding the benefits will allow for an appropriate cost-benefit analysis of how vector control treatments can be utilized for the optimization of resources. This will help the World Health Organization and the governments of burdened countries in their objective of reducing malaria incidence on a global scale.

Objective

The objective of the systematic review was to determine the impact of combined ITN and IRS on malaria prevalence and incidence.

Methods

Overview of PRISMA Guidelines

Guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used to conduct the systematic review. PRISMA is a minimum set of items that guide the methods of reporting in systematic reviews. While the majority of the guidelines were followed in the making of this review, some of the items were excluded due to practicality restraints. In particular, items 5 (protocol and registration), 12 (risk of bias in individual studies), 15 (risk of bias across studies), 16 (additional analyses), and 27 (funding). These items were not included in the review because they were either sufficiently covered in other sections, or were not applicable to the present review.[18]

Search Process

In order to acquire a comprehensive overview of current literature, systematic search methods and specific inclusion criteria were established. Selected articles were limited to those written in English, published between 2012 and 2017, and found in the National Center for Biotechnology Information (NCBI). The specific search terms used to identify articles were as follows:

"Combination of Insecticide Treated Nets and Indoor Residual Spraying for Malaria"

This search yielded several results, which were further evaluated based on exclusion criteria to determine if they were to be included in the review. After removing articles based on exclusion criteria (see below), the remaining studies were then evaluated via full-text analysis. Studies from this group were further eliminated due to insufficient sample size, study design limitations,

and irrelevant study outcomes. For example, studies that investigated the entomological outcomes of combining ITNs and IRS were excluded from the review, as the focus of this particular review was to determine the impact on humans, rather than the malaria vectors.

Exclusion Criteria

In 2014, the World Health Organization (WHO) performed a review a current literature speculating the combination effect of insecticide treated nets (ITNs) and indoor residual spraying (IRS). Several of the research groups involved in the studies that were reviewed have continued their research in more recent years. These articles in addition to those groups' previous studies were included in this review in order to compare the trends seen in each study. In narrowing down the initial search results down, previous systematic reviews as well as reviews of unrelated subjects were excluded (n = 35). Articles that were published prior to 2012 were excluded in the review, in order to acquire current and relevant studies on the subject of interest. Studies that examined entomological outcomes were also excluded, as this review was interested in identifying medical outcomes. Furthermore, all review articles were excluded. Lastly, only articles that performed statistical analyses to determine the effect of combining IRS and ITN interventions were included in this review. Of note, the studies included in the final review consisted of both randomized trials and observational studies. No exclusion criteria were placed on study type because data can be extracted from both types of studies.

Data Collection Process and Items

Results from each selected study were abstracted by the researcher via independent full text analysis. Specifically, malaria frequency, measure(s) of association, p-values for statistical

analysis, and 95% confidence intervals were abstracted for further analysis in the review. In addition to these data, information such as study population, the area studied, the pesticides utilized, and the size of study clusters (if applicable) were abstracted to further characterize the quality of the selected studies.

Results

Study Selection

After performing the initial search with the terms as specified above, 254 results were obtained from the PubMed database. After excluding reviews, studies pertaining to subjects irrelevant to the review, and articles falling outside of the inclusion criteria, 23 articles remained for full-text analysis. Full-text analysis allowed for the exclusion of three articles due to insufficient sample size, five articles due to study design limitations, and five articles due to conclusions irrelevant for the review. This resulted in a total of 10 articles being included in final review (Figure 2).

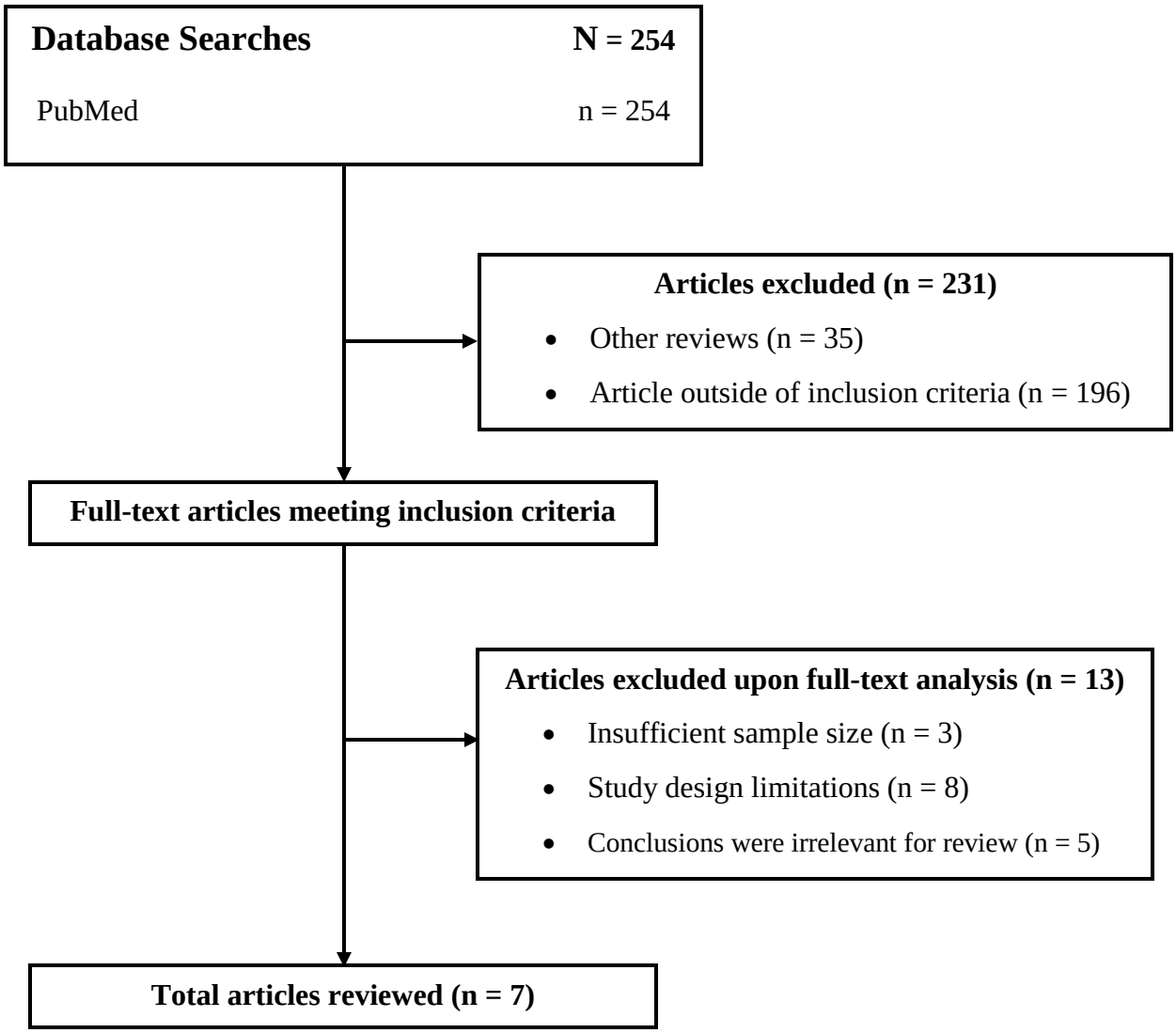

Figure 2 – Illustration of process utilized for acquiring the studies discussed in this review.

Results of Individual Studies (Randomized Trials)

1. Ethiopia (Bekele et al., 2012)

This study consisted of three study arms with three clusters per arm, giving nine clusters in total. The study was done over the course of five months in three *kebeles* (smallest administrative unit in Ethiopia) of similar populations in the district of Adami Tulu. In each arm, the malarial prevalence among children under five years of age (first cluster), the malarial prevalence among individuals over 15 years of age (second cluster), and the overall malarial prevalence of the population (third cluster) were measured. One study arm consisted of the population receiving neither ITNs nor IRS, and took place in the *kebele* of Jela Aluto. The second study arm consisted of ITN treatment, where two ITNs were provided per household in the *kebele* of Kamo Gerbi. Finally, the third study arm consisted of ITN treatment, again with two nets per household, and was combined with DDT at a dosage of 2 g/m^2.[19] The results of each of these study arms are summarized in Table 1.

Table 1. Prevalence Rates of Malaria in Children Under 5 Years, Over 15 Years, and Overall

Area	Study Arm	Prevalence Rate (%)	p – value
Jela Aluto	No Treatment	26.2 (under 5 years)	$p < 0.05$
		9.5 (over 15 years)	$p < 0.05$
		10.4 (overall)	$p < 0.05$
Kamo Gerbia	ITNs	6.0 (under 5 years)	$p < 0.05$
		10.2 (over 15 years)	$p < 0.05$
		5.4 (overall)	$p < 0.05$
Anemo Shisho	ITNs + IRS	1.2 (under 5 years)	$p < 0.05$
		3.7 (over 15 years)	$p < 0.05$
		1.7 (overall)	$p < 0.05$

This study concluded that there was a significant reduction malaria prevalence between the population that received no treatment and the population that received ITNs. Furthermore, this

study reports that there was a significant added benefit to combining ITNs and IRS versus ITNs alone. In the *kebeles* of Kamo Gerbi (ITNs) and Aneno Shisho (ITNs + IRS), the authors of this study state that the lower prevalence rate in children under five compared to individuals over 15 years is likely due to the fact that children under five were more frequently allowed to utilize the treated nets.[19]

2. Zambia (Hamainza et al., 2016)

In this study, the districts of Luangwa and Nyimba in Zambia were selected for research, as these districts had pre-existing rates of ITN usage (81.7%). In each of these districts, seven clusters of about 165 households were selected and enrolled in the study. Deltamethrin (IRS), lambdacyhalothrin (IRS), or no supplemental vector control method was randomly applied to the 14 clusters, resulting in a quasi-randomized study. Diagnostic positivity of the participants tested for malaria was then recorded over the course of 29 months. During this period, three sequential applications of the different treatments were applied, allowing for a longitudinal study of the different treatments. Of note, because each cluster received some form of IRS at some point during this study, there was no true control group present over the course of this study.[20] The results of the study are summarized in Table 2.

Supplementing pyrethroids-treated ITNs with additional pyrethroids via IRS added short-lasting, incremental benefits as opposed to using ITNs alone. It is stated that this added benefit is likely the result of "…reduced vector population density, human exposure to bites, and to sporozoite inoculations." However, following three months of IRS treatment, the incremental benefit due to combining vector control methods failed to be observed. Regarding the benefits of adding IRS to

these ITN covered areas, the authors concluded that pirimiphosmethyl EC provided the greatest added benefit, followed by lambdacyhalothrin CS, which provided a greater benefit than deltamethrin WG. In addition to the previously described conclusions, this study was also able to conclude that supplementing these ITNs with non-pyrethroid IRS allowed for mitigation of insecticide-resistant vectors.[20]

Table 2. Diagnostic Positivity in Areas with Pre-existing ITN Coverage after Receiving IRS Treatment

Cluster	October 2010 – March 2011		October 2011 – March 2012		October 2012 – March 2013	
	IRS Treatment	DP %	IRS Treatment	DP %	IRS Treatment	DP %
1	None	24.7	None	9.5	None	14.4
2	None	20.9	Pirimiphosmethyl EC	8.5	None	11.9
3	None	26.9	None	10.8	None	14.1
4	Deltamethrin WG	33.2	Pirimiphosmethyl EC	5.9	Pirimiphosmethyl EC	10.8
5	Deltamethrin WG	27.5	Pirimiphosmethyl EC	18.2	Pirimiphosmethyl EC	27.8
6	Deltamethrin WG	11.9	Lambdacyhalthrin CS	5.2	Lambdacyhalthrin CS	3.8
7	Deltamethrin WG	6.0	Lambdacyhalthrin CS	4.2	Lambdacyhalthrin CS	2.99
8	None	55.7	None	29.9	Pirimiphosmethyl EC	9.0
9	None	36.4	Pirimiphosmethyl EC	46.6	Pirimiphosmethyl EC	23.5
10	None	50.7	None	35.4	Pirimiphosmethyl EC	27.1
11	None	51.3	Pirimiphosmethyl EC	30.2	None	11.9
12	None	61.9	None	33.9	Pirimiphosmethyl EC	21.7
13	None	60.0	Pirimiphosmethyl EC	27	None	30.6
14	None	52.4	None	41.3	Pirimiphosmethyl EC	16.99

3. Gambia (Pinder et al., 2014)

This study was comprised of two-arm cluster, randomized trials in several Gambian villages. The villages were ensured to be at least two kilometers away from each other in order to avoid spillover of trial participants. The study arms of this research consisted of: (1) ITNs alone and (2) ITNs with IRS with the pesticide dichlorodiphenyltrichloroethane (DDT). From the selected villages, children aged six months to 14 years old were divided into a total of 70 clusters, with each cluster containing between 65 and 213 children. Incidence of malaria was then measured in passive case detection. Children with one malaria attack, children with more than one malaria attack, and incidence of malaria per child-month at risk were measured for both study arms. These data were then quantified using an unadjusted rate ratio with a 95% confidence interval. This was done both in 2010 and in 2011.[21] The results of this statistical analysis are displayed in Table 3.

The results of this study showed that in areas with high ITN coverage, there was no significance difference observed in malaria transmission between groups that had received IRS treatment, and those that did not. Therefore, it was concluded that combining treatments offered no added benefit to ITNs alone. It has been suggested that a combination of a persistent insecticide with ITNs would allow communities within Gambia to reduce malaria transmission to pre-elimination levels.[21] However, based on the conclusions of this study, the authors recommended against this action.

Table 3. Case Detection in Children in Clusters with ITNs Alone Versus IRS plus ITNs

Passive Case Detection	2010		2011		Unadjusted Rate Ratio (95% CI)	
	ITNs (n = 3942)	IRS plus ITNs (n = 3887)	ITNs (n = 3837)	IRS plus ITNs (n = 3820)	2010	2011
Children with one malaria attack	450/3942 (11%)	409/3887 (11%)	543/3837 (14%)	520/3820 (14%)	0.92 (0.81 – 1.05)	0.96 (0.86 – 1.08)
Children with more than one malaria attack	33/3942 (1%)	23/3887 (<1%)	58/3837 (2%)	50/3820 (1%)	0.71 (0.42 – 1.20)	0.87 (0.60 – 1.26)
Incidence of malaria per child-month at risk	0.0468 (0.0336 – 0.0658)	0.0442 (0.0333 – 0.0587)	0.0321 (0.0255 – 0.0404)	0.0341 (0.0259 – 0.0452)	0.94 (0.61 – 1.46)	1.06 (0.74 – 1.46)

4. Tanzania (Protopopoff et al., 2015)

In this study, two rounds of IRS with bendiocarb insecticides in combination with universal coverage of ITNs was compared with ITNs alone in a cluster randomized trial. This took place between April 2011 and December 2012. Sampling was performed on eight houses within 20 clusters per study arm, and occurred for one night per month. Besides vector density, entomological inoculation rate was also sampled as a measurement associated with malaria prevalence. There was evidence that entomological inoculation rate was lower in the intervention arm (IRS + ITNs) versus the control arm (ITNs alone). Additionally, there was evidence that the effect of combining both treatments was higher in the low vector density clusters versus the high density clusters. This difference was determined to be statistically significant based on a 95% confidence interval and an interaction p-value < 0.001.[22] These results are displayed in Table 4.

Table 4. Inoculation Rate with Entomological Indicators

		ITNs			**ITNs + IRS**	
Outcome	**Total Houses**	**Mean**	**[95% CI]**	**Total Houses**	**Mean**	**[95% CI]**
Mean Culex/house/night	1055	3.8	[2.3 – 6.1]	1120	2.7	[1.8 – 4.1]
Mean *An. Gambiae* s.l/house/night	1055	3.1	[1.0 – 9.6]	1120	2.2	[0.5 – 9.1]
EIR/house/month		1	[0.4 – 2.8]		1.3	[0.4 – 4.4]

From the data, this study concluded that "…in an area of northern Tanzania two rounds of carbamate IRS combined with a moderate coverage of ITN produced a reduction in Anopheles density and entomological inoculation rate of public health importance compared to use of ITN

alone." The authors also conclude that this effect "…can account for the 57% reduction in malaria infection prevalence observed in the combination arm of this trial."[22]

5. Tanzania (West et al., 2015)

This study consisted of a cluster randomized trial in which 50 clusters had already received ITNs from a universal coverage campaign. Of these clusters, 25 were randomly selected to receive two rounds of IRS with pyrethroid lamdacyhalothrin during the year of 2012. 80 households were contained within each cluster, resulting in a total of 4000 households being involved in this study. Three surveys were conducted to test for the presence of the malaria parasite in children between the ages of 0.5 years old and 14 years old. This was quantified as *Plasmodium falciparum* prevalence rate (*Pf*PR). The first survey took place two months after the first round of IRS, the second survey was conducted six months after the first round and two months after the second round, and the third survey was conducted ten months after the first round and six months after the second round. Statistical analysis to test for the presence of an impact was carried out using a 95% confidence interval, an unadjusted odds ratio, and an adjusted odds ratio.[23] These results are displayed in Table 5.

Table 5. Effect of Village IRS and individual net use on *PfPR*, adjusted for other risk factors

	PfPR	**Unadjusted Odds Ratio**	**Adjusted Odds Ratio**
	% [95% CI], (n)	**OR, [95% CI], p-value**	**OR, [95% CI], p-value**
Study arm			
ITNs only	26.1, [16.7, 38.4], (6315)	1.00	1.00
ITNs + IRS	13.3 [7.9,21.5], (6831)	0.43. [0.19-0.97], p = 0.0434	0.41, [0.29-0.58], p < 0.0001
Individual net use			
No	19.1, [13.4-26.5], (7511)	1.00	1.00
Yes	19.9, [13.6-28.1], (5635)	1.05, [0.84-1.32], p = 0.0428	0.83, [0.70-0.98], p = 0.0305
Survey			
Post Intervention A	18.4, [13.3-25.0], (4533)	1.00	1.00
Post Intervention B	21.3, [14.9-29.4], (4237)	1.20, [0.99-1.45]	1.23, [0.92-1.65]
Post Intervention C	18.7, [12.3-27.4], (4376)	1.02, [0.83-1.26], p = 0.0551	0.87, [0.66-1.15], p = 0.0525
Baseline Malaria Prevalence			
Per 10% increase		2.05, [1.85-2.28], p < 0.0001	2.04, [1.85-2.25], p < 0.0001
Individual age (years)			
0.5 – 4	18.1, [12.4-25.6], (4745)	1.00	1.00
5 – 9	21.1, [14.8-29.2], (4819)	1.21, [1.06-1.39]	1.56, [1.32-1.83]
10 – 14	19.0, [13.3-26.4]. (3582)	1.07, [0.88-1.29], p < 0.0001	1.57, [1.28-1.91], p < 0.0001

Several conclusions were made as a result of this study. Namely, this study concluded that individuals who reported using both IRS and ITNs together were more protected than those using ITNs alone. The authors of this study add that there was no significant difference in the effect of combining IRS and ITNs between low and high transmission areas. Finally, the authors also mention that IRS provided protection both at the house-hold level (individuals living in sprayed homes) and at the community level, even if certain individuals did not live a household that received spraying.[23]

Results of Individual Studies (Observational Studies)

1. Kenya (Gimnig et al., 2016)

This study consisted of three cross-sectional surveys that were performed in two districts. The Rachuonyo District (the IRS district), had received one round of IRS spraying with pyrethroid insecticides between July and September of 2008. This was then followed by a second round of IRS spraying in April 2009. Data collected from the cross-sectional surveys in the IRS district was compared to data collected from the Nyando district (the non-IRS district). The first cross-sectional survey served as a baseline, and was conducted prior to the first round of spraying in the IRS district. The second and third surveys were then conducted in November 2008 (three months after the first round of IRS) and August 2009 (four months after the second round of IRS).

During each cross-sectional survey, participants in the study were interviewed and asked whether they had utilized an ITN the previous night. This allowed the researchers to divide the acquired data into four categories: (1) ITNs and IRS, (2) ITNs alone, (3) IRS alone, and (4) neither

treatment. Odds ratios were utilized to make comparisons between each category of treatments and its impact on malaria prevalence. The group receiving neither treatment was used as the reference.[24] These results are summarized below in Table 6.

Table 6. Odds Ratios in Areas with Combined Treatments Versus One Treatment Alone, Measured After One and Two Rounds of IRS

Parameter	Odds Ratio (After 1st Round of IRS)	P – value	Odds Ratio (After 2nd Round of IRS)	P – value
ITNs + IRS	0.14	P > 0.05	0.58	P > 0.05
IRS	1.71	P > 0.05	0.47	P > 0.05
ITNs	0.95	P > 0.05	0.59	P < 0.05
No Treatment	1	P > 0.05	1	P < 0.05

The authors of this study concluded that adding the treatment of IRS in an area where there is already moderate ITN coverage provided a reduced prevalence of malaria. However, they added that there is not as clear of a benefit when ITNs are added to an area that has already received IRS treatment.[24]

2. Uganda (Katureebe et al., 2016)

Katureebe et al. (2016) performed an observational study between October 2011 and March 2016 of three sub-counties within the country of Uganda. The three sites that were observed had varying levels of malaria transmission. Walukuba had relatively low levels of transmission, Kihihi had moderate levels, and Nagongera had the highest levels of transmission. Between 2013 and 2014, campaigns were spearheaded by the Ugandan government and distributed ITNs

throughout all three sub-counties in this study. Furthermore, IRS using carbamate bendiocarb as an insecticide was applied to the sub-county of Nagongera.

The ITN distribution campaign markedly increased the amount of access to nets. The proportion of households that had at least one ITN increased from 49.0% to 65.0% in Walukuba, 37.5% to 86.5% in Kihihi, and 71.0% to 95.5% in Nagongera. The IRS application in Nagongera resulted in the 78% coverage of the sub-county with IRS. For each area, the incidence of malaria was quantified by measuring the adjusted rate ratio on a 95% confidence interval.[25] Specifically, the adjusted rate ratio measured in each of these regions compared malaria incidence before and after receiving ITNs. A fourth adjusted rate ratio was then measured in Nagongera to compare malaria incidence with ITNs alone and with a combination of ITNs and IRS. Therefore, only one area assessed the efficacy of combining vector control treatments. The results of this statistical analysis are displayed in Table 7.

Table 7. Adjusted Rate Ratio in Areas Receiving ITNs Alone and ITNs plus IRS

Study Site	Treatment	Adjusted Rate Ratio (95% CI)	P – value
Walukuba	ITNs	1.02 (0.36 – 2.91)	P = 0.97
Kihihi	ITNs	0.65 (0.43 – 0.98)	P = 0.04
Nagongera	ITNs	1.10 (0.76 – 1.56)	P = 0.60
	ITNs + IRS	0.13 (0.07 – 0.27)	P < 0.001

The conclusions from this study were that ITNs combined with IRS provide an extremely large reduction in the incidence of malaria compared to ITNs alone (ARR = 0.13). However, can only be claimed for areas with relatively high transmission rates of the disease. Because IRS was only applied in the sub-county of Nagongera, the effect of combining ITNs and IRS in areas with low or moderate malaria transmission rates was not measured.[25]

Discussion

Summary of Evidence

After reviewing all studies involved in the systematic review, six out of the seven studies indicated an added benefit to combining ITNs and IRS treatments. From the summarized data, displayed in Table 8, this added benefit does not appear to be dependent on the coverage of ITNs or IRS. However, in both observational studies performed, a significant reduction in the frequency of malaria was seen when IRS was applied to areas that had already been distributed ITNs. This could imply that the efficacy of these treatments is lowered when they are applied simultaneously. One possible explanation for this could be that sudden exposure of the mosquitoes to both treatments promotes a higher degree of insecticide resistance than being exposed to one treatment at a time. For the study taking place in Gambia, performed by Pinder et al. (2014), relatively high rates of both ITNs and IRS were reported and no significant effect was seen by the authors in this study. However, in the study performed by Hamainza et al. (2016) in Zambia, a relatively low rate of IRS was utilized and a significant added benefit was observed. It is important to note that for both of these studies, *Plasmodium falciparum* Prevalence Rate (PfPR) was not reported. Because of this, the conclusions made by both of these studies may be limited.

Interestingly, all studies that were mentioned in this review compared ITNs + IRS to ITNs alone. No study attempted to compare ITNs + IRS to IRS alone. The observational study performed by Gimnig et al. (2016) mentions the idea of adding ITNs to areas already covered by IRS, but they stated that they were unable to make any conclusive remarks on whether this would add any benefit. The fact that there were no published studies comparing both treatments to IRS alone

may be due to the mere feasibility. Providing individuals with ITNs may be logistically more simple than engaging in a campaign that involves the indoor spraying of households. Therefore, it may have been more common for the researchers involved in these studies to provide ITNs to both groups, versus engaging in indoor spraying for both the control and experimental groups.

Table 8. Summary of Randomized Trials and Observational Studies

Comparison	IRS Insecticide	Clusters per Arm	Vectors	Reported ITN Coverage	Reported IRS Coverage	*PfPR*	Age Groups Studied	Result
Ethiopia								
ITNs + IRS vs ITNs vs No Treatment	DDT	3	*Anopheles gambiae, Anopheles pharoensis*	50% - 65%	Not reported	*PfPR* = 1.3% (No Treatment) *PfPR* = 4.4% (ITNs) *PfPR* = 8.6% (ITNs + IRS)	Under 5 years old, Over 15 years old	Significant effect
Zambia								
ITNs + IRS vs ITNs	Pyrethroid	Quasi-randomization	*Anopheles funestus*	> 80%	40%	Not reported	All ages	Significant effect
Gambia								
ITNs + IRS vs ITNs	DDT	35	*Anopheles gambiae*	> 90%	> 80%	Not reported	0.5 – 14 years old	No significant effect
Tanzania								
ITNs + IRS vs ITNs	Bendiocarb	20	*Anopheles gambiae, Anopheles arabiensis*	> 90%	> 85%	*PfPR* = 23%	Under 15 years old	Significant effect
Tanzania								
ITNs + IRS vs ITNs	Pyrethroid	25	*Anopheles gambiae, Anopheles arabiensis*	> 90%	90%	*PfPR* = 13.3% (ITNs + IRS) *PfPR* = 26.1% (ITNs)	0.5 – 14 years old	Significant effect

Table 8 cont. Summary of Randomized Trials and Observational Studies								
Comparison	**IRS Insecticide**	**Clusters per Arm**	**Vectors**	**Reported ITN Coverage**	**Reported IRS Coverage**	***PfPR***	**Age Groups Studied**	**Result**
Kenya								
ITNs + IRS vs ITNs vs IRS	Pyrethroid	No randomization	*Anopheles gambiae, Anopheles arabiensis*	Moderate (55% - 65%)	60%	*PfPR* = 1.8% (Non-IRS District) *PfPR* = 4.9% (IRS District)	All ages	Significant effect
Uganda								
ITNs + IRS vs ITNs	Bendiocarb	No randomization	*Anopheles gambiae*	65% - 95%	> 90%	*PfPR* = 16%, 18% (ITNs) *PfPR* = 60% (ITNs + IRS)	0.5 – 10 years	Significant effect

There is some debate as to whether combining ITNs and IRS has a greater benefit in areas where the rate of malaria transmission is high. West el at. (2016) concluded that there was no significant difference seen between areas of low and high transmission when both treatments were combined. However, this is contrasted with the conclusions made by Katureebe et al. (2016), who concluded that a significant added effect is seen *only* in areas where the transmission rate is high. No other studies provided data or conclusions on the difference in effect between areas of varying transmission rates. Therefore, no conclusive statements may be made from this review on this particular factor.

In past reviews, there has been no clear trend of significant benefits being observed by combining ITNs and IRS. This review, however, provides a new perspective into this subject matter. While the circumstances for each study vary, the majority of the studies analyzed in this review state that an added benefit exists. This may indicate that investing in universal coverage programs within the region of Sub-Saharan Africa may allow the countries involved to reduce the transmission rates of malaria to elimination.

Limitations of the Review

Although a thorough search and analysis of recent studies was performed in the systematic review, there are several areas in which this review may be limited. Namely, additional relevant studies may not have been detected or obtained for a variety of reasons. The amount of studies reviewed may be limited by the databases that were searched. Only PubMed was utilized during the acquisition of studies pertaining to the effect of combining ITNs and IRS. While this database is fairly extensive, it is likely not complete and therefore, there is a possibility that

additional articles may have been overlooked. Furthermore, this review is limited in the fact that only studies presented in English were obtained. It is entirely possible that studies investigating ITNs and IRS may have been initially published in a language other than English, and have not been translated at this time. It is also important to realize that this review focused on studies that involved medical outcomes of combining ITNs and IRS, and actively excluded those pertaining to entomological outcomes. While this was convenient for narrowing the focus of this study, entomological outcomes may also provide good indications into the benefits provided by combining vector control methods.

Lastly, the systematic review may be limited by region. Although the continent of Africa experiences by far the highest rate of malaria prevalence, Southeast Asia and South America also are significantly burdened by malaria. Studies performed in these regions may provide additional data regarding the factors affecting the efficacy of utilizing both treatments versus one.

Conclusions

This systematic review provided insights that had not yet been seen within previous reviews on the combination effect of ITNs and IRS. This provides a promising perspective as the WHO continues its effort to reduce the prevalence of malaria in endemic countries. The countries in which these studies were performed will likely experience an increase in population within the coming decades, and it will be important to take an aggressive stance on controlling the spread of this disease. From an economic standpoint, it would be wise to carefully plan where and when to apply ITN and IRS campaigns, as some countries will be more predisposed to high transmission rates of malaria than others. Because of this, future randomized trials investigating ITNs and IRS

should be performed within the region of Sub-Saharan Africa. In addition to studying the combination effect, these studies should make an effort to discern the impact that transmission rate has on the efficacy of both vector control treatments. This will provide additional findings that will help determine an effective strategy for the application of ITNs and IRS in the future.

While other groups investigating malaria vector control may use the discussed findings to guide their future studies, the insights provided by this review may also be used by the governments of endemic countries and non-governmental organizations (NGOs) working towards reducing the incidence of malaria. As discussed above, the observational studies reviewed indicate that combining vector control treatments is more effective when the area receiving this intervention has already been utilizing ITNs. This finding should obviously be investigated further, but for now it may serve as a guide for any group that is considering implementing IRS in a region. By using this information, NGOs that wish to begin further ITN distribution campaigns may coordinate both with researchers and the governments of burdened countries. This will allow for IRS and ITNs to be implemented at times that maximize their effectiveness of vector control.

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