ORIGINAL ARTICLE

Economic Evaluation of Oral Ivermectin, Alone or in Combination with Permethrin, versus Permethrin, in the Treatment of Classic Scabies in the Philippine Setting

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ABSTRACT

Background and Objective. Oral ivermectin is recommended as an alternative to topical permethrin in Japanese, European, and CDC-STI guidelines for treating classic scabies. The combination of oral ivermectin and topical permethrin is also used in some settings. Partial economic evaluations conducted in India and Egypt have conflicting results, and no cost-effectiveness analysis in the Philippines has compared ivermectin-based regimens to permethrin for scabies treatment. We aimed to determine the cost-effectiveness of oral ivermectin, alone or in combination with permethrin, compared to permethrin, in the treatment of Filipino adult patients with classic scabies.

Methods. We used a decision tree model to estimate the cost-effectiveness of two regimens, oral ivermectin alone or in combination with permethrin, compared with permethrin to treat adults and children aged five years and older with classic scabies in the outpatient setting from the household perspective in the Philippines. We estimated total costs and disability-adjusted life years (DALYs) over a one-month follow-up. Input parameters were obtained from secondary data, such as effect estimates for probabilities of clinical outcomes from a network meta-analysis, DALYs from the Global Burden of Disease 2019, and prevailing market cost in the Philippines (DPRI 2022 with recommended markup by DOH, and leading drugstores) as of August 2022. We computed for incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) to determine which of the interventions are cost-effective. Univariate and probabilistic sensitivity analyses, and scenario analyses were conducted to assess the impact of parameter and structural uncertainty.

Results. Ivermectin-based regimens are suggested to be likely cost-saving compared to permethrin in the Philippine outpatient setting. Base case analysis showed that oral ivermectin had higher cost-savings (change in cost, -1,039.31; change in DALYS, 0.00027), while combination oral ivermectin/permethrin had higher DALYs averted (change in cost, PhP -1,019.78; change in DALYs, 0.00045), compared to permethrin. Combination oral ivermectin/permethrin (56%) was the most cost-effective, followed by oral ivermectin (44%) compared to permethrin (0%) through probabilistic sensitivity

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analysis. Estimates for ivermectin were sensitive to risk of cure for ivermectin vs permethrin using 1-way deterministic sensitivity analysis. Oral ivermectin was favored over combination oral ivermectin/permethrin at all thresholds based on the cost-effectiveness acceptability curve.

Conclusion. Both ivermectin-based regimens seem to be cost-saving compared to permethrin in the treatment of classic scabies in the Philippine outpatient setting. Clinicians may consider oral ivermectin, alone or in combination with permethrin as an alternative first-line or second-line treatment depending on patient preference, adverse event risk profile, availability, and economic capacity. This needs to be confirmed using primary data from Filipino patients to enhance the robustness of the findings and support evidence-based local decision-making in different settings. Less uncertainty in modelled parameters can give greater confidence in the results, which can be adopted for budget impact analysis and allow more rational resource allocation. Value of information analysis can be done to determine whether the expense of future RCTs or surveys in Filipinos to collect primary data is worth it. The cost of reducing uncertainty, if deemed worth the cost of further studies, may facilitate population-level decision-making and budget planning. Findings may further inform practice guideline development, coverage decisions, and national control program planning by providing the most cost-effective scabies intervention.

Keywords: scabies, ivermectin, permethrin, economic evaluation, cost-effectiveness

INTRODUCTION

Scabies is a highly contagious and extremely itchy ectoparasitic skin infection caused by the mite, *Sarcoptes scabiei var hominis.*[1] If left untreated, scabies can continue for many months and become secondarily infected. In severe and untreated cases, these may result in septicemia and acute post-streptococcal immune sequelae, such as rheumatic fever and acute glomerulonephritis.[2]

It was recently included as a neglected tropical disease (NTD) by the World Health Organization (WHO) in 2017 as it was found to affect 200 million people at any time, especially children (~10%) in resource-poor areas.[3] Prevalence estimates in the recent scabies-related literature range from 0.18% to 71%.[4] It contributed the 2nd highest disability among all skin diseases [DALYs of 129 (95% CI, 71, 208) per 100,000] for the Philippines based on the Global Burden of Disease (GBD) study 2019.[5] Age-specific global prevalence for scabies showed an increasing trend from age 5 to 25, then at age 70 years.[6] Scabies ranked fourth among new consults with an overall median percentage of 5.15% (IQR 2.35) from 2010-2021 in dermatology training outpatient departments (OPDs) in the Philippines based on the Philippine Dermatological Society Health Information System.[7]

The most common first-line of treatment for scabies are topical prescription scabicides such as permethrin 5%, benzyl benzoate 25%, or crotamiton 10%.[8] Most drugs work through a neurotoxic mechanism either by delayed repolarization (permethrin, malathion, lindane) or hyperpolarization (ivermectin) in neuromuscular synapses, thereby paralyzing and killing the mites. However, there is generally low compliance with topical treatments due to the arduous task of applying the cream, repeat treatments, skin irritation, itching, malodour, and the high cost.[9] Oral ivermectin is a broad spectrum antiparasitic used since the 1980s for onchocerciasis control programs[10] that was first approved for scabies in Europe in 2001. European,[11] Japanese,[12] and US CDC-STI[13] guidelines also recommend oral ivermectin as an alternative to permethrin as first-line treatment of classic scabies. The most recent systematic reviews suggested oral ivermectin and topical permethrin to be comparable for clinical cure outcome based on a 2018 Cochrane systematic review with a pairwise meta-analysis (oral ivermectin vs permethrin, RR 0.91, 95% CI 0.76, 1.08; 2-week timepoint; 5 RCTs, N = 459; low certainty evidence).[14] A 2019 network meta-analysis showed similar effect estimates for permethrin vs oral ivermectin (network RR 1.03, 95% CI 0.96, 1.11; 3 to 6 weeks timepoint; 52 RCTs, N = 9917; no rating of evidence certainty).[15] An unpublished network meta-analysis (NMA) (Genuino, unpublished study) similarly suggested comparable efficacy at 1 to 2 weeks post-treatment (oral ivermectin vs permethrin, network RR 0.95, 95% CI 0.89, 1.02; 30 RCTs, N = 3469; low certainty evidence).[16]

A 2019 effectiveness review by the Canadian Agency for Drugs and Technologies in Health (CADTH) that searched between January 1, 2014 to April 17, 2019 included three systematic reviews/meta-analyses (including a 2019 NMA), one RCT, and three clinical practice guidelines (CPGs) (European and Japanese).[17] They concluded that oral ivermectin may be less clinically effective than topical permethrin in the first one to two weeks following treatment but there is no difference at later timepoints (four weeks onwards). They also stated that there is no difference in adverse events between the two interventions. They noted that there are no cost effectiveness studies comparing ivermectin (topical/oral) vs scabicides such as permethrin. The WHO applied to include scabies as an indication for oral ivermectin in its List of Essential Medicines in 2018. Although they stated that no cost benefit analyses have been carried out focusing on the use of ivermectin in scabies, it is likely that effective interventions with ivermectin may reduce personal, institutional, and governmental expenditure.[18]

The WHO recommends the use of oral ivermectin for scabies mass administration programs in high prevalence (>10%) areas.[19] For prevalence between 2 and 10%, intensified disease management, which is clinical case detection

and treatment of close contacts, was recommended as an alternative strategy, subject to refinement with future data. Oral ivermectin is off-label for scabies in the Philippines, like in the USA, UK, and Canada. It was listed in the Philippine National Formulary[20] for filariasis and was again recommended as an alternative anti-filarial drug for the national filariasis control program by the Philippine Department of Health (DOH) in 2021.[21] The human preparation was first registered in the Food and Drug Administration (FDA) in May 2021 as an anti-nematodal.[22] In April 2023, an interim guidance was issued by the Philippine DOH that recommends topical scabicides listed in the PNF 2019 (permethrin, benzyl benzoate, crotamiton, and sulfur) as the first-line treatment but that oral ivermectin may be used off-label in scabies for treatment failure or intolerance with topical scabicides, immunosuppressed or those with crusted scabies, and outbreak settings.[23] Although oral ivermectin is listed in the PNF Essential Medicines List 2019,[24] it is unlisted in the main PNF 2019 and its Philippine FDA registration has expired as of November 2022.[25]

Common adverse effects of permethrin are mostly cutaneous and include mild and transient burning and stinging, itching, skin redness, skin swelling, or skin rash, and may be treated with topical steroids.[26] On the other hand, those reported with oral ivermectin are mostly systemic and include pruritus, fever, rash, myalgia, headache, and can usually be treated with aspirin, acetaminophen, and antihistamines.[27] Serious neurological adverse events such as encephalopathy and seizures have been reported but are hypothesized to be due to drug-drug interactions and rare genetic mutations of a transporter protein that enables ivermectin to enter blood-brain barrier.[28,29] In addition, although ivermectin has been shown to have few and mild adverse events among children weighing less than 15 kg (based on a systematic review of 14 observational studies and 1 RCT, N = 1088)[30] and inconclusive evidence on safety in pregnant women (based on a systematic review of 5 observational studies and 1 RCT, N = 893),[31] its contraindication in these vulnerable groups needs further elucidation. The direct cost of a pack of 100 tablets of ivermectin is approximately US$2.90 with a unit price of US$0.029 per tablet, with cost subject to variations in different countries.[32]

Combination oral ivermectin and topical scabicides is also a common off-label prescription even in classic scabies, especially among severe and extensive scabies. Usage of the combination oral ivermectin and topical permethrin among surveys of general practitioners (GPs) ranged from 26% (France)[33] to 80.5% (Germany),[34] and 45% -59% (US dermatology OPDs).[35,36] A two-dose regimen of each was recommended by the Austrian Society for Dermatology and Venereology in 2019 as a modified off-label regimen until the 'epidemic' is controlled.[37] In a 2019 network meta-analysis (NMA),[15] the combination regimen (single dose of oral ivermectin and permethrin) ranked highest in efficacy with acceptable safety, but this was based only on one RCT.[38]

The economic burden of scabies outbreaks can be substantial, with an average cost per scabies outbreak of around US$25 000 in a systematic review of 14 publications.[39] The largest cost was an outbreak of scabies in a Canadian long-term care facility in August 2003 that started from two index cases (one classic and one crusted scabies) and cost the facility CDN$200,000 and negative publicity.[40] A systematic review of published scabies transmission models and data to evaluate cost-effectiveness of scabies interventions recommends supplementing model input parameters with locally specific data collections and expert opinion as appropriate.[41] Previous trial-based cost-analyses showed variable results, with lower cost per patient cured for oral ivermectin compared to permethrin in India[42,43] and Egypt[44] while the opposite findings were found by two other RCTs that included cost of oral antihistamine[45,46] and transportation.[45] A higher cost for combination therapy compared to permethrin and oral ivermectin was shown in a three-arm RCT in India that only used single dose of each regimen.[38]

There is no Philippine cost-effectiveness study comparing these ivermectin-based regimens to permethrin in the treatment of scabies. We aimed to conduct a cost-effectiveness analysis for oral ivermectin alone or in combination with topical permethrin versus topical permethrin as a first-line treatment using the intensified disease management approach in the treatment of non-pregnant Filipino adults and children weighing more than 15 kg with classic scabies in the Philippine setting.

METHODS

This economic evaluation, which is based on a decision analytic model, is part two of a four-part thesis dissertation on the comparative effectiveness of oral ivermectin, alone or combined with permethrin, vs permethrin alone, by the primary author. The study protocol was approved by the ethics board (UPM-REB 2022-0055-01). Part one is a systematic review and network meta-analysis on clinical efficacy and safety; parts three and four are qualitative studies on patient and physician acceptability. The protocol contained a health economic analysis plan and is available upon request. This paper used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist.

We used a model-based rather than a trial-based economic evaluation since we did not plan to conduct an RCT due to physical limitations and restrictions of the COVID-19 pandemic. We specified the population, intervention, comparator, outcome, and time horizon (PICOT) components of the decision analytic model (Table 1). We only included immunocompetent, non-pregnant, non-lactating adults and children 15 kg and above with classic scabies of any severity as the target population, since oral ivermectin is not recommended for pregnant/lactating women and children below 15 kg. We assumed that the patients and their household contacts had no comorbidities

Table 1. Summary of PICO Characteristics of Decision Analytic Model

PICOT Characteristic	Description
P – Patient population/setting	Immunocompetent, non-pregnant, non-lactating (adults and children at least 15 kg body weight) patients with classic scabies, any severity, without bacterial superinfection; outpatient setting, Philippines
I – Interventions	1) Oral ivermectin (two-dose); 2) Combination oral ivermectin and permethrin (one dose each)
C – Comparator	Permethrin (two-dose)
O – Outcomes	DALYs averted, Number of patients cured

(including bacterial co-infection) and no concomitant medications that may interact with oral ivermectin intake at the start. Two ivermectin-based regimens (2-dose ivermectin alone, or single-dose combination oral ivermectin/permethrin) were considered as the interventions, and were compared with 2-dose permethrin, the standard of care. Oral ivermectin was given once a week for two weeks; permethrin was given as whole-body overnight application for 8 to 12 hours in two weekly doses; and the combination regimen was given simultaneously as a single dose of each intervention. In addition, they were managed at the outpatient setting and did not get hospitalized. We used a patient payor perspective since intensified disease management of scabies recommends that close contacts of the index case are treated simultaneously, whether with scabies or not. Thus, the other household members may participate in the expenses aside from the index case. In addition, the costs of outpatient treatment of scabies are not covered by PhilHealth nor provided freely by local health centers. Household out-of-pocket payment made up almost half of the health expenditure in the Philippines (41.5% of Filipinos as of 2021).[47] We set the willingness-to-pay (WTP) threshold at PhP 177,350.625 (US$ 3460.5 [GDP per capita, as of 2021] x 51.25 PhP/US$ as of December 31, 2021).[48,49]

Model Overview and Assumptions

We used a decision tree model to compare the costs and outcomes of three alternatives for the first-line treatment of classic scabies (Figure 1):

1. oral ivermectin 200 mcg/kg (two doses given one week apart)
2. combination oral ivermectin 200 mcg/kg and permethrin 5% lotion (one dose each, given at the same time)
3. Permethrin 5% lotion (2 doses, 1 week apart)

The decision tree is the simplest form of decision analytic modelling but may become too complicated if there a lot of branches representing different event possibilities. We used a decision tree model and not a Markov state transition model since we chose to model the acute infestation stage of scabies; we did not include systemic post-infectious immune sequelae involving the kidney and heart since there is no local data. We also excluded recurrences after initial cure based on the experience of the expert panel in the local outpatient setting wherein they do not usually see recurrences among treated patients even up to a year or more after successful treatment. Scabies is a curable disease and although scabies may be recurrent in endemic communities, most of the recurrences are due to reinfestations from untreated contacts, poor compliance, or improper administration.

In a decision tree model, the decision node (= square) represents the point wherein a decision is made between the three treatments. The chance node (= circle) represents the possible logical events in the alternate treatment pathways. The terminal node (= triangle) represents the endpoints or final outcomes, to which the costs and effects are assigned. Assumptions and formulas used to populate the model were validated by an expert panel (composed of clinicians and health economists) and are given in Appendix 1.

We did not do any subgroup analysis to explore possible heterogeneity since we do not have separate treatment effects for different subgroups [e.g., children and adults; high income vs low- to middle-income countries (LMIC)] from the unpublished NMA; most of the included studies were on adults and in LMIC. No distributional analyses were done to explore the effects of altering socioeconomic differences on the health equity impact plane.

Resource Use and Costs

Costs consisted of direct medical, direct non-medical, and indirect costs, in Philippine peso (PhP), based on the latest 2021 Philippine Drug Price Reference Index (DPRI 2021 9th ed)[50] (with recommended markup based on DOH guidance)[51] as well as current leading drugstore prices (as of August 2022) for the cost estimates. The direct medical costs for treatment were computed based on scabicides, adjunctive anti-itch treatment, treatment of bacterial infection and adverse events, and professional fee of physicians. The direct non-medical costs included laundry cost and transportation cost, while indirect cost was from lost wages. To compute for the cost of scabicides, we assumed an intensified disease management approach treating both the index patient and three household contacts based on average Filipino household size of 4.1 (2 adults and 1 child)[52] of the index patient using the same treatment regimen. Prophylactic treatment of close contacts, even if asymptomatic, is part of the intensified disease management strategy by WHO to control transmission and prevent reinfection of index case.[19] Oral antihistamines and topical steroids to treat pruritus were computed for the index case only, assuming that household members are asymptomatic. Patients who fail treatment were assumed to continue to develop new scabies lesions and bacterial coinfection with 5% requiring oral antibiotics (based on expert panel opinion). We assumed moderate cellulitis and computed the cost of antibacterial treatment using a thrice-daily regimen of cefalexin for one week. For

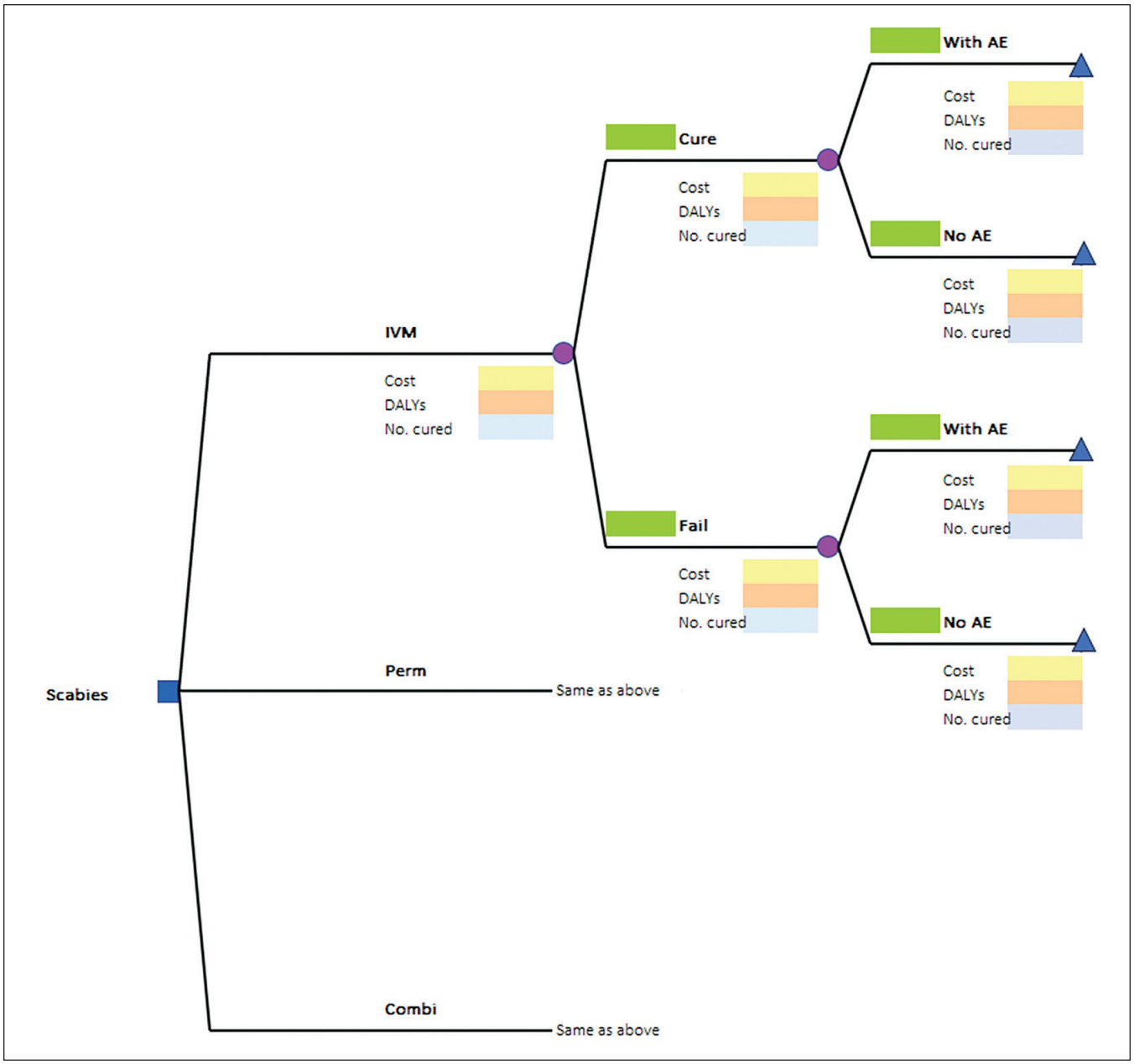

Figure 1. Decision tree model for scabies treatment.

IVM, Ivermectin; Perm, Permethrin; Combi, Combination treatment; AE, Adverse event; DALYs, Disability-adjusted life years.

Note: Assumptions and formulas for the model are in Appendix 1.

the cost of treatment failure, we also added the cost of an extra dose of oral ivermectin, permethrin, or both (for combination regimen). The cost of treating adverse events were computed with the assumption of the most common adverse events based on pairwise meta-analysis from a previous systematic review (Part 1 of this author's dissertation) (Genuino et al., 2022); moderate contact dermatitis (cutaneous adverse event) and mild headache (systemic adverse event). We prorated the cost of treating adverse events by multiplying the proportion of those with systemic adverse events (oral ivermectin, 0.3793; combination regimen, 0.4000; permethrin, 0.1795) and those with cutaneous adverse events (oral ivermectin, 0.6207; combination regimen, 0.6000; permethrin, 0.8205) with the cost of treatment for headache and dermatitis, respectively.

Direct non-medical cost was computed based on transportation and an additional batch of laundry as part of the environmental control to eliminate mite reservoirs. The cost of transportation was based on the average distance from a health facility using the rates of three common modes of

transport (jeepney, light rail transit, and taxi) in the National Capital Region. Laundry was assumed to be three-day worth of clothes and bedding for all four household members. The cost was derived from three self-serve laundromats in three metropolitan areas in the Philippines (Metro Manila, Metro Cebu, and Metro Davao). Indirect cost consisted of lost wages and we assumed it to be for two days for patient or caregiver of patient (if patient was a child). There will be no need to do discounting, which is done to reflect the loss in economic value that occurs when there is a delay in realizing a benefit or incurring a cost, since we used a decision tree model. Table 2 and Appendix 2 show these costs and sources of data.

Table 2. Input Parameters

Parameters	Base Case	Lower Limit	Upper Limit	Standard Error	Distribution	Source
Probabilities/Relative Risks						
Relative risk of cure with 2-dose oral IVM vs 2-dose permethrin (rCureIVM)	1.1200	0.9900	1.2800	0.0655	lognormal	Genuino et al., 2022 (split dose network), (Appendix 2)
Relative risk of cure with 1-dose combination oral IVM/permethrin vs 2-dose permethrin (rCureCombi)	1.2100	0.9400	1.5600	0.1292	lognormal	Genuino et al., 2022 (main network), (Appendix 2)
Probability of cure with 2-dose permethrin (pCurePerm)	0.8200	0.6700	0.9200	0.0510	beta	Genuino et al., 2022 (proportional one-arm meta-analysis for 2-dose permethrin) (Figure A3.1; Appendix 3)
Probability of cure with 2-dose Oral IVM (pCureIVM)	0.9184	0.8118	1.0000	0.0416	beta	Multiplying rCureIVM with pCurePerm Upper limit was truncated at 1.0
Probability of cure with 1-dose Combination oral IVM/permethrin (pCureCombi)	0.9922	0.7708	1.0000	0.0040	beta	Multiplying rCureCombi with pCurePerm Upper limit was truncated at 1.0
Probability of failure with 2-dose permethrin (pFailPerm)	0.1800	0.0800	0.33	0.0765	beta	Subtracting pCurePerm from 1.0
Probability of failure with 2-dose oral IVM (pFailIVM)	0.0816	0.0718	0.087312	0.0029	beta	Subtracting pCureIVM from 1.0
Probability of failure with 1-dose Combination oral IVM/ permethrin (pFailCombi)	0.0078	0.0072	0.010374	0.0013	beta	Subtracting pCureCombi from 1.0
Risk Ratio of Adverse Events with IVM 2-dose vs Permethrin 2-dose (rAEIVM)	0.2700	0.1200	0.6000	0.4106	lognormal	Genuino et al., 2022 (splitdose network), (Appendix 3)
Risk Ratio of Adverse Events with Combination IVM/Permethrin 1-dose vs Permethrin 2-dose (rAECombi)	0.3300	0.0800	1.4400	0.737339734	lognormal	Genuino et al., 2022 (splitdose network), (Appendix 3)
Probability of Adverse Events with permethrin (2-dose) (pPermWithAE)	0.0542	0.0366	0.0769	0.0116	beta	Genuino et al., 2022 (proportional meta-analysis for adverse events wit 2-dose permethrin) (Figure A4.2, Appendix 4)
Probability of Adverse Events with Oral IVM (pIVMWithAE)	0.0331	0.0206	0.0526	0.0100	beta	Multiplying rAEIVM with pPermWithAE
Probability of Adverse Events with Combination Oral IVM/ permethrin (pCombiWithAE)	0.040	0.010	0.173	0.0401	beta	Multiplying rAECombi with pPermWithAE
Probability of No Adverse Events with Oral IVM (pIVMNoAE)	0.9669	0.9474	0.9794	0.0064	beta	Subtracting pIVMWithAE from 1.0
Probability of No Adverse Events with Combination Oral IVM/permethrin (pCombiNoAE)	0.9637	0.8851	0.9886	0.0127	beta	Subtracting pCombiWithAE from 1.0
Probability of No Adverse Events with permethrin (pPermNoAE)	0.9458	0.9231	0.9634	0.0090	beta	Subtracting pPermWithAE from 1.0

Table 2. Input Parameters *(continued)*

Parameters	Base Case	Lower Limit	Upper Limit	Standard Error	Distribution	Source
Cost*						
Direct Medical Cost						
Cost of treatment with oral IVM (2-dose) for index case (cIVM)	37.63	36.27	39.94	1.1781	Gamma	Leading Drugstores (Mercury Drug, Rose Pharmacy, Watsons Drug)
Cost of treatment with permethrin (2-dose) for index case (cPerm)	185.70	177.31	193.97	4.219	Gamma	DPRI 2021 9th ed with markup; Leading Drugstores (Southstar Drug, Watsons Drug)
Cost of treatment with combination oral IVM/ permethrin for index case (1-dose each) (cCombi)	111.66	106.79	116.95	2.6986	Gamma	See above
Cost of treatment of three household members with Oral IVM (cIVMHH)	115.42	111.25	122.50	3.6139	Gamma	Mercury Drug, Watsons Drug, Southstar Drug
Cost of treatment of three household members with permethrin (cPermHH)	569.63	543.90	595.00	12.9421	Gamma	DPRI 2021 9th ed with markup; Southstar Drug, Watsons Drug
Cost of treatment of three household members with Combination oral IVM/ permethrin (cIVMHH)	342.53	327.58	358.75	8.2781	Gamma	See above for oral IVM and permethrin
Cost of treating headache in index case (systemic adverse events) (cHeadache)	36.53	11.30	59.62	11.7821	Gamma	Syrup (DPRI 2021 9th ed with markup; RiteMed, Southstar Drug) Tablet (DPRI 2021 9th ed with markup; Southstar Drug, Watsons Drug)
Cost of treating moderate dermatitis in index case (Cutaneous adverse event) (cDermatitis)	1431.99	697.44	1,933.72	255.9832	Gamma	Betamethasone propionate (DPRI 2021 9th ed with markup; RiteMed, Watsons Drug) Clobetasol propionate (DPRI 2021 9th ed with markup; Southstar Drug, Watsons Drug)
Cost of treating bacterial infection (Moderate cellulitis) (for 5% of index cases with treatment failure) (cBactInf)	540.82	152.65	987.82	228.0660	Gamma	DPRI 2021 9th ed with markup; RiteMed, Watsons Drug
Cost of adjunctive diphenhydramine for index case (cDiphen)	225.7185	49.5501	453.75	116.3430946	Gamma	Syrup (DPRI 2021 9th ed with markup; Southstar Drug, Rose Pharmacy) Tablet (DPRI 2021 9th ed with markup; Watsons Drug, Rose Pharmacy)
Cost of adjunctive topical steroids for index case (cTopSter)	1431.9949	697.4388	1933.7220	255.9832	Gamma	Betamethasone cream (DPRI 2021 9th ed with markup; RiteMed, Watson's Drug) Clobetasol cream (DPRI 2021 9th ed with markup; Southstar Drug Watsons Drug)
Cost of professional fee of physician for two visits of index case (cPF)	1000.0000	500.0000	1,500.00	255.1020408	Gamma	PCP-AHMOPI PAHMOC MOA; medicalpinas.com; Personal communication with physicians
Direct Non-medical Cost						
Cost of laundry for three days for index case and three household contacts (cLaundry)	744.0000	630.0000	810.0000	33.67346939	Gamma	Bubble-Up; Suds Davao; Soak N Relax
Cost of transportation for index case and companion for two physician visits (cTranspo)	201.3333	88.0000	352.0000	76.8707483	Gamma	Jeepney fare; LRT fare; GrabCar
Indirect Cost						
Cost of lost wages of index case or caregiver for two days (cLostWages)	885.0000	630.0000	1140.0000	130.1020408	Gamma	DOLE Minimum Wage (Region VIII; Region XI; NCR)

Table 2. Input Parameters *(continued)*

Parameters	Base Case	Lower Limit	Upper Limit	Standard Error	Distribution	Source
DALY weights						
DALY weight for cure (DALY_Cure)	0.0000	0.0000	0	0	constant	IHME GBD 2019
DALY weight for failed treatment (DALY_Scabies)	0.0270	0.0150	0.042	0.007653061	beta	IHME GBD 2019
DALY weight for mild contact dermatitis (cutaneous adverse event) (DALY_Dermatitis)	0.0270	0.0150	0.042	0.007653061	beta	IHME GBD 2019
DALY weight for tension headache (systemic adverse event) (DALY_Headache)	0.0370	0.0220	0.057	0.010204082	beta	IHME GBD 2019
DALY for moderate cellulitis (bacterial infection) (for 5% of failed treatment) (DALY_BactInf)	0.0510	0.0320	0.074	0.011734694	beta	IHME GBD 2019

IVM, Ivermectin; DALY, Disability-adjusted life years; DPRI, Drug Price Reference Index; IHME, Institute of Health Metrics; GBD, Global Burden of Disease

*Note: *Costs for the index patient was prorated based on age distribution of patients with scabies in the Philippine Dermatological Society database 2010-2021 (each cost is a sum of the cost of treating a child multiplied by 0.37 and the cost of treating an adult multiplied by 0.63); Base case for cost was computed using the average value of three different sources, while upper limit was the highest and the lower limit was the least of the three costs; Cost of adverse events was prorated based on percentage of patients with cutaneous or systemic adverse events from the unpublished NMA in primary author's dissertation (Appendix 4); Detailed assumptions are in Appendix 1.*

Probabilities for the Treatment Effects

We based the probabilities and relative risks for treatment effects on the systematic review and network meta-analysis from the unpublished NMA in principal author's dissertation (PROSPERO 2022 CRD42022278007), published literature, or consensus from an expert panel. The treatment effects for oral ivermectin, topical permethrin, and combination treatment included benefits (i.e., clinical cure) and harm (adverse events) and can be found in Table 2. Clinical cure was defined in the NMA as resolution of scabies lesions, with or without resolution of symptoms such as itch, with or without parasitological cure via microscopy of skin scrapings, dermoscopy, or other imaging. Adverse events were defined as "any untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine."[53] We used the split dose network estimates from the unpublished NMA [i.e., relative risk (RR)] effect estimate from the two-dose oral ivermectin vs two-dose permethrin comparison, and the single-dose combination oral ivermectin/permethrin vs two-dose permethrin comparison to closely approximate the dosing regimens in our model (Appendix 2). The exception was for the RR for clinical cure of combination oral ivermectin/permethrin (single dose) vs permethrin wherein main analysis was used (different doses of permethrin) since the base probability would exceed 1.0. By multiplying the relative risk of effects with the baseline risk with permethrin (two-dose) from the proportional one-arm meta-analysis (Appendix 4),[54] we derived the probabilities of cure or adverse events for oral ivermectin and combination ivermectin/permethrin. We prorated the cutaneous (e.g., dermatitis) and systemic (e.g., headache) adverse event rates for oral ivermectin and combination oral ivermectin/permethrin by using the percentage of patients with each type of adverse event among the total number of patients with adverse events from the pairwise meta-analysis of oral ivermectin vs permethrin, and combination oral ivermectin/permethrin vs permethrin, respectively.[16] We multiplied these prorated adverse event rates with the cost of treatment for each type of adverse event.

Health Utility Weights/Number Patients Cured

The disability adjusted life years (DALY) utility weights were taken from the GBD 2019.[55] We assumed a DALY weight of zero for those who were cured, 0.027 for those who failed treatment and continued to have scabies (rest of DALY weights are in Table 2). We prorated the DALYs by dividing by 12 (for the DALYs from bacterial infection and scabies, assuming that the disability lasted 1 month in 1 year) and by 52 (for the DALYs from headache or dermatitis, assuming that the disability lasted for 1 week in 1 year).[27] When the outcome was a combination of two outcomes (e.g., treatment failure leads to scabies and bacterial infection; adverse events may be both headache and dermatitis) which had no assigned DALY weights from GBD 2019, we computed for the combined DALY weight using the formula recommended for a multiplicative approach:[56]

$$\text{combined DALY weight} = 1 - (1-DW1)*(1-DW2)$$

where DW1 = utility weight of 1st event (e.g., treatment failure); DW2 = utility weight of 2nd event (e.g., adverse event).

However, this multiplicative approach is only recommended for two co-existing medical conditions and cannot be applied for patients who fail treatment (1st event) and continue to have scabies and develop bacterial infection, who also develop adverse events (2nd event), which can be both cutaneous (dermatitis) and systemic (headache). For patients who failed treatment (1st event) who remain to have scabies and develop bacterial co-infection, we used the higher DALY weight between scabies (DALY weight, 0.027) and moderate cellulitis (DALY weight, 0.051) for the 1st event. Similarly, for the 2nd event, there are no assigned DALY weights for the combined adverse events of headache and dermatitis from GBD 2019; thus, we assumed the higher of the DALY weights for headache (0.037) and dermatitis (0.027), which is that of headache. To test the robustness of using this DALY weight approach to combined medical conditions, we conducted a scenario analysis wherein we reversed the sequence of methods for accounting for the combined DALY weights; we used the multiplicative approach first before choosing the higher of the two combined DALY weights.

Running the Pharmacoeconomic Analysis

We ran the decision analytic model using Microsoft Excel and used inputs of the probabilities of treatment outcomes (clinical cure, adverse events), costs, and either utility weights for DALYs (cost-utility analysis) or number of patients cured (cost-effectiveness analysis). The number of patients cured was derived by multiplying the number of patients (assuming one patient entering the model) by the proportion of cure with each intervention.

We computed for the incremental cost-effectiveness ratio using the following formula:

$$\text{ICER} = \frac{(\text{cost of intervention X} - \text{cost of comparison intervention Y})}{(\text{effect of intervention X} - \text{effect of comparison intervention Y})}$$

The effects of intervention in the denominator were either number of patients cured or DALYs, and the units for ICER was in PhP/number of patients cured or PhP/DALYs. Based on the cost-effectiveness plane, we determined if the two ivermectin-based regimens are less costly and more effective [i.e., dominant or cost-saving, southwest (SW) quadrant], which means it should be adopted; or more costly and less effective [i.e., dominated, northwest (NW) quadrant], in which case it should not be adopted. When the ICER is negative, and it lies in the northeast (NE) quadrant or southeast (SE) quadrant, it is considered cost-effective when it lies to the right of the willingness-to-pay (WTP) line. When an intervention was dominant (less costly, more effective) or dominated (more costly, less effective), there was no need to compare the ICER to the WTP.

Uncertainty and Scenario Analysis

We conducted univariate (individual parameters, one at a time) and probabilistic (across all parameters simultaneously) sensitivity analyses to determine parameter uncertainty. We presented the results of univariate sensitivity analysis using tornado diagrams. We conducted a probabilistic sensitivity analysis using Monte Carlo simulation with 10,000 runs of the model and used a scatter plot to display the cost-effectiveness plane. We used recommended distributions for health economic evaluation, namely, gamma distribution for costs, beta distribution for DALY weights and probabilities, and lognormal distribution for the risk ratios.[57] We also tested the impact of varying WTP thresholds in a cost-effectiveness acceptability curve.

We conducted the following scenario analyses: 1) assumed varying compliance than 100% (assumption in main analysis) for permethrin (70%), ivermectin (95%), and combination (82.5%), and 2) doing the multiplicative approach between combined DALY weights of scabies and bacterial infection, and those of dermatitis and headache, before getting the higher DALY weight of the two combined DALY weights as the final combined DALY weight for the model.

RESULTS

Base Case Analysis

Using a patient perspective wherein the cost of treatment is paid out-of-pocket, both oral ivermectin and combination treatment were cost-saving compared with permethrin. Using base case analysis, for patients with classic scabies treated with oral ivermectin alone, there was lower cost compared with permethrin (incremental cost, PhP -1,039.31), greater DALYs averted (incremental DALYs, 0.00027), and more patients cured (incremental number of patients cured, 0.073). For those treated with combination therapy, compared to permethrin, there was also lower cost (incremental cost, PhP -1,019.78), greater DALYs averted (incremental DALYs, 0.00045), and more patients cured (incremental number of patients cured, 0.103). There was a similar trend for the outcome of the number of patients cured. Table 3 summarizes the cost-effectiveness analysis results using the base case values.

Using Monte Carlo simulation for probabilistic sensitivity analysis, the cost-effectiveness plane shows the incremental costs and incremental DALYs generated for ivermectin, and combination therapy compared with permethrin. Around 56% of the iterations fell on the two quadrants on the right hand of the plane for combination ivermectin/permethrin, 44% for oral ivermectin, and none for permethrin (Figure 2).

In all ceiling ratio values, oral ivermectin and combination therapy remained more cost-effective than permethrin (Figure 3).

One-way Sensitivity Analysis

For oral ivermectin, ICER was sensitive to the relative risk of cure for ivermectin vs permethrin (% change in ICER, 91.58%), shown in the tornado diagram (Figure 4).

For the combination therapy, ICER was not sensitive to any parameters as shown in the tornado diagram (Figure 5).

Scenario Analyses

When we conducted two scenario analyses, 1) varying compliance rates, and 2) doing the multiplicative approach between DALY weights of scabies and bacterial infection, and those of dermatitis and headache, before getting the higher DALY weight of the two combined DALY weights, the conclusion did not change and both ivermectin-based regimens remained cost-saving compared to permethrin (Table 4). For the varying compliance scenario, however, there was a shift from base case analysis in that oral ivermectin now had higher cost savings (-1,885.11 PhP) and more DALYs averted (0.00076) compared to combination treatment (-1,307.40 PhP; 0.00063 DALYs averted).

DISCUSSION

The results of this study suggest that both oral ivermectin (two-dose) and combination oral ivermectin/permethrin (single dose each) are cost-saving compared to permethrin in adult patients and children weighing more than 15 kg with classic scabies who are managed in the outpatient setting in the Philippines using a patient perspective. Our result is consistent with several published RCTs that showed a lower cost per patient cured for ivermectin vs permethrin[38,42–44] In contrast, two studies[45,46] that conducted a trial-based cost-effectiveness analysis showed the opposite finding of permethrin having a lower cost per patient cured. While Chhaiya et al.[45] likewise included transportation to the drug cost, similar to our study, Munge et al. did not.[46] The main difference with our results and that of these two studies is that they included the cost of antihistamine. Our study did not include itch resolution as an outcome since the evidence from the unpublished NMA of the primary author's dissertation was very low quality, mainly due to heterogeneity in outcome measurement and variation in the adjunctive treatments for itch. Thus, we just gave a blanket symptomatic treatment regimen of two weeks of oral antihistamine and topical steroids to all patients, assuming that all exhibited itching. The treatment regimen used by Chhaiya et al.[45] was the flexible dosing regimen

Table 3. Summary of Cost-effectiveness Analysis Results (Base Case Analysis)

Base case values	Ivermectin vs Permethrin	Combination vs Permethrin	Permethrin
Total costs (PhP)	4,221.46	4,240.99	5,260.77
Total DALYs	0.00021	0.00003	0.00048
Total number cured	0.97	0.90	1.0
Change in cost (PhP)	-1,039.31	-1,019.78	
Change in outcomes (DALY averted)	0.00027	0.00045	
ICER per DALY averted (PhP/DALY averted)	-3,850,919.87	-2,271,842.00	
Change in outcomes (No. of cured patients)	0.07369	0.10253	
ICER per patient cured (PhP/Patient cured)	-14,103.41	-9,945.73	

DALY, Disability-adjusted life year; ICER, Incremental cost-effectiveness ratio

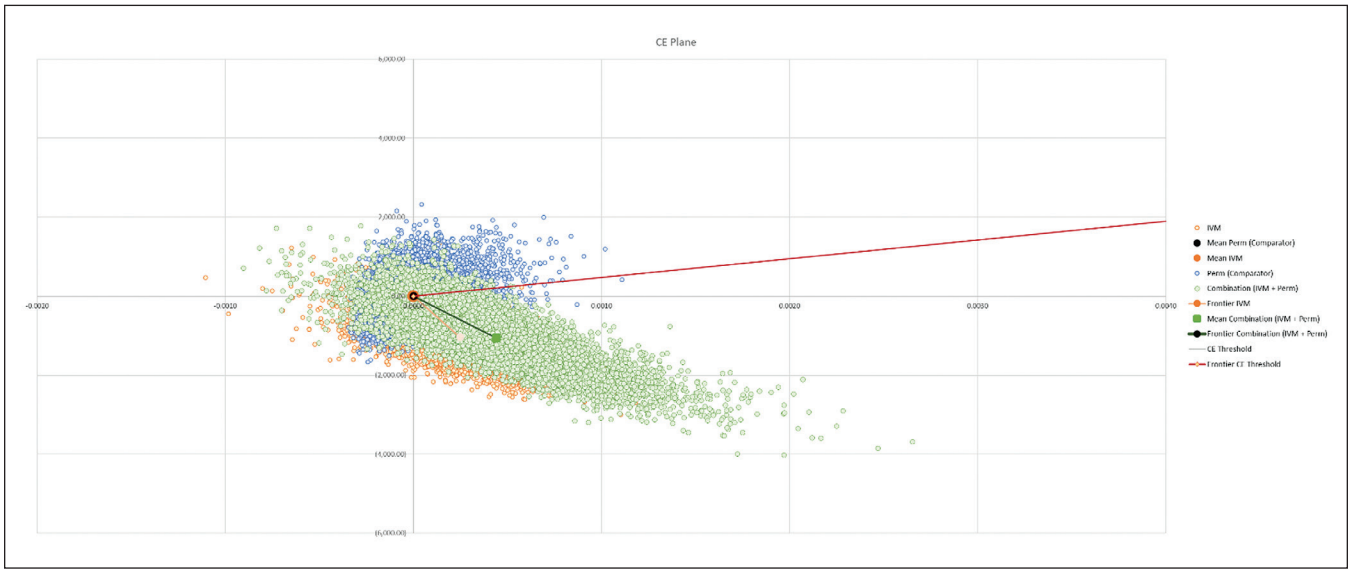

Figure 2. Cost-effectiveness plane (probabilistic sensitivity analysis).

IVM, Ivermectin.

wherein patients with clinical cure at earlier timepoints (one, two weeks) did not proceed to receive additional doses up to three weeks. Our study used the two-dose regimen for both oral ivermectin and permethrin while a single dose for the combination regimen. Chhaiya et al.,[45] however, did not consider other indirect costs such as lost wages and treatment of household members and environmental disinfection. Health outcomes (e.g., quality-adjusted life years, QALYs or DALYs) were not considered in the cost-effectiveness equation, unlike our study where we used DALYs. Adverse events and its treatment were likewise excluded in their model. Differences in drug and transportation costs in India

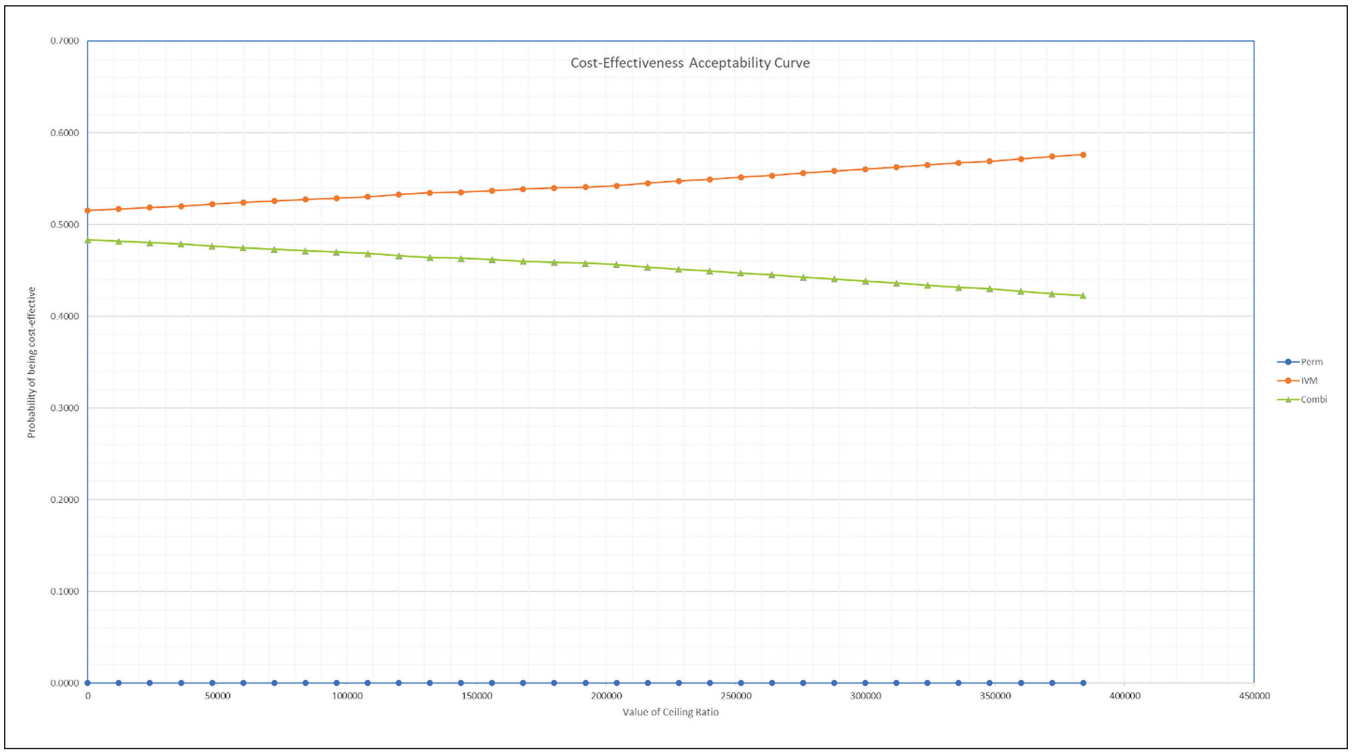

Figure 3. Cost-effectiveness acceptability curve for oral ivermectin vs combination treatment vs permethrin (base case analysis).

Perm, Permethrin; IVM, Ivermectin; Combi, Combination.

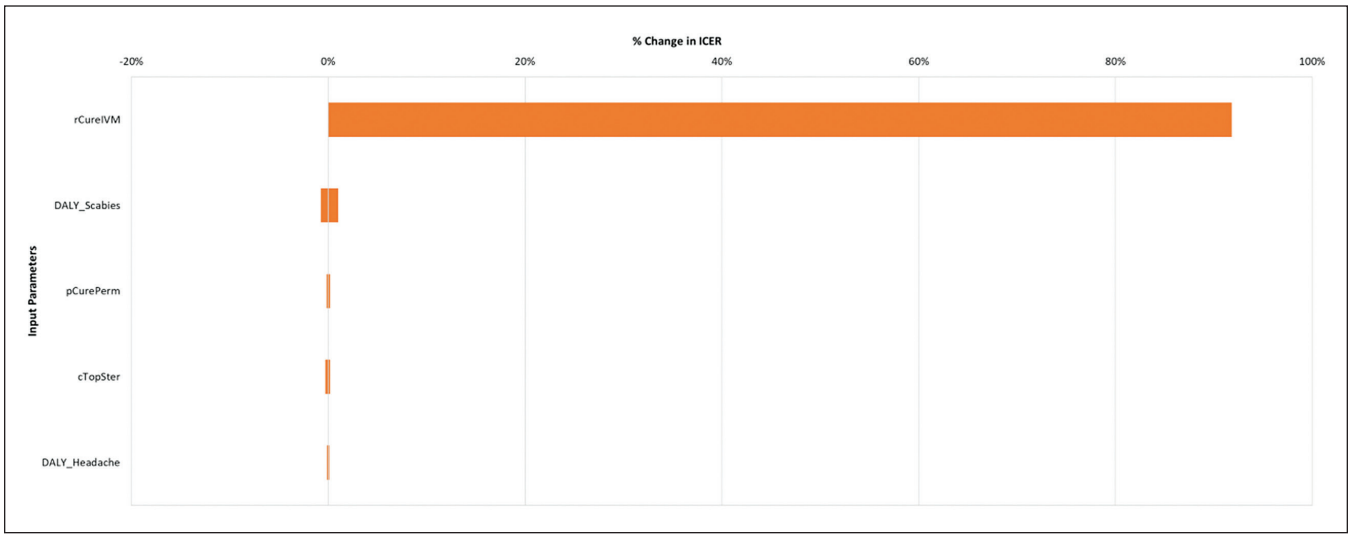

Figure 4. One-way deterministic sensitivity analysis: Tornado diagram (Ivermectin vs permethrin).

rCureIVM, relative risk of cure for oral ivermectin vs permethrin; DALY_Scabies, disability-adjusted life years for scabies; pCurePerm, Probability of cure with permethrin; cTopSter, cost of topical steroids; DALY_Headache, disability-adjusted life years for headache.

vs the Philippines may also account for the discrepancy. Our results for combination treatment differed from the trial-based cost-effectiveness analysis by Wankhade et al.[38] that showed combination treatment to have the highest cost per patient cured (Rs 75.58, end of one week; Rs 67.70 Rs, end of four weeks) compared to permethrin (Rs 70.51, end of one week; Rs 61.11, end of four weeks).

The initial flooding of the Philippine market with oral ivermectin, driven by high demand during the COVID-19 pandemic, was replaced a slowly dwindled supply as COVID-19 cases dropped. From more than 15 distributors at the height of the pandemic, it has now been reduced to only two (as of 17 June 2023). Thus, the local availability of ivermectin may be a logistical problem despite the promising results of this cost-effectiveness analysis.

Among the parameters used in the study, the risk of cure for ivermectin vs permethrin was a major cause of uncertainty in our analysis. The unpredictability in these variables may be due to clinical heterogeneity that was evident among the included studies in the network meta-analysis. However, these potential differences in risk factors such as severity of scabies infestation, primary vs recurrent scabies, and outcome definitions for cure, were not fully explored due to lack of subgroup data. Although the point estimates used in the study based on low-certainty evidence from a network meta-analysis may still reasonably reflect the relative treatment effects of the interventions for these outcomes, we recommend value of information analysis. By comparing the expected value of a decision with perfect information (EVPI) to the expected value of a decision with the existing uncertainty,

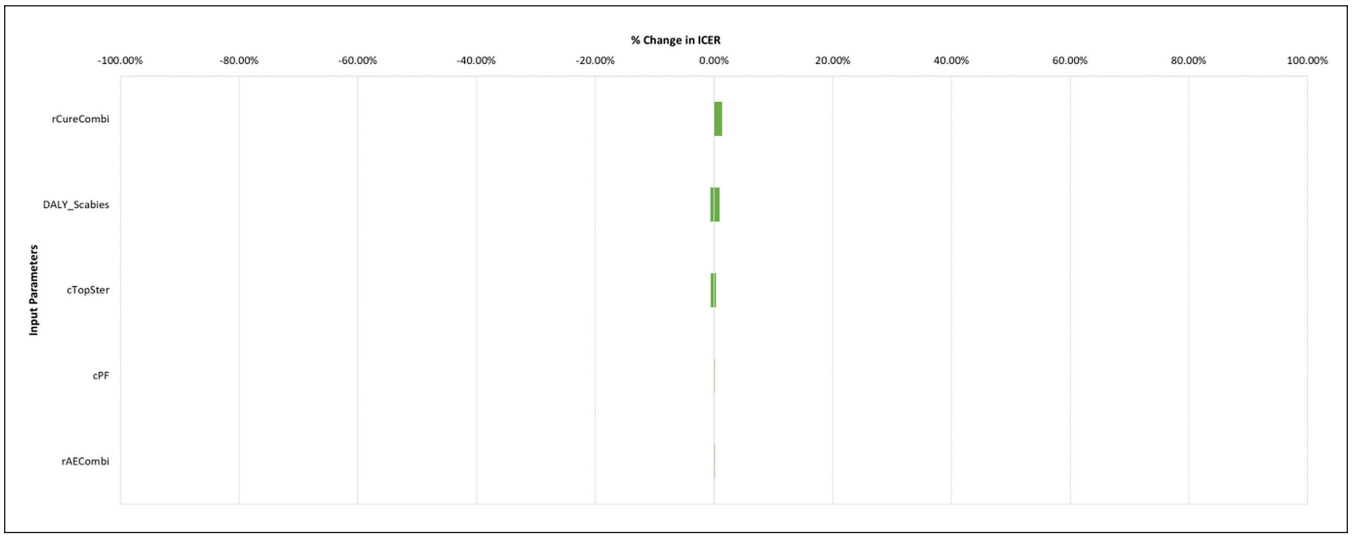

Figure 5. One-way deterministic sensitivity analysis: Tornado diagram (Combination therapy vs permethrin).

CureCombi, relative risk of cure for combination oral ivermectin/permethrin vs permethrin; DALY_Scabies, disability-adjusted life years for scabies; cTopSter, cost of topical steroids; cPF, cost of professional fee of physician; rAECombi, relative risk of adverse events for combination oral ivermectin/permethrin vs permethrin.

Table 4. Summary of Results for Scenario Analyses

Deterministic results	Ivermectin vs Permethrin	Combination vs Permethrin	Permethrin
Scenario using lower compliance			
Total costs (PhP)	4,398.58	4,976.28	6,283.69
Total DALYs	0.00032	0.00046	0.00109
Change in cost (PhP)	-1,885.11	-1,307.40	
Change in outcomes (DALYs averted)	0.00076	0.00063	
ICER per DALY averted (PhP/DALYs averted)	-2,475,805.72	-2,086,355.11	
Scenario using multiplicative DALY weights for each combined outcome*			
Total costs (PhP)	4,221.46	4,240.99	5,260.77
Total DALYs	0.00021	0.00003	0.00047
Change in cost (PhP)	-1,039.31	-1,019.78	
Change in outcomes (DALY averted)	0.00026	0.00044	
ICER per DALY averted (PhP/DALY averted)	-3,939,639.43	-2,306,924.91	

DALYs, Disability-adjusted life years; ICER, Incremental cost-effectiveness ratio
**combined DALY weights for dermatitis and headache; combined DALY weights for scabies and bacterial infection*

the difference between these two values represents the potential value that additional information could provide.[58]

This study has several strengths. First, the clinical cure and adverse event rates were derived from a pooled network meta-analysis that used data from the two-dose ivermectin, two-dose permethrin, and single-dose combination treatment network comparison. We assumed that the Philippine setting would have similar efficacy and safety data as the pooled studies from the NMA as most of the studies were conducted in a LMIC. As the known scabicidal effect of ivermectin is believed to be dependent on the need for a second dose to kill the newly hatched mites from eggs, treatment effects from single dose ivermectin regimens, if lumped with the multiple dose regimens, would necessarily be disadvantageous for ivermectin and may have underestimated the ICERs.

We note some limitations in our analysis. Firstly, our model did not include itch resolution, as the unpublished NMA (in dissertation of principal author) only performed a pairwise meta-analysis showing unclear effects on itch resolution (very low certainty evidence). We did not perform a network meta-analysis for itch resolution due to high heterogeneity. In addition, this outcome has not been measured by the two RCTs that compared combination treatment with permethrin. Itch resolution rates and differential use of oral antihistamine/topical steroids should be measured in local RCTs and included in future economic models. Secondly, we lumped together all age groups (children 5 to 18 y/o; adults 19 y/o and older) since we did not have subgroup data on clinical outcome rates from the NMA stated earlier. Subgroup analysis for relevant age groups and clinical severity is recommended for future RCTs. For the public health aspect, we recommend mapping out the age-specific prevalence of scabies in the country and do budget impact analysis for different prevalence-based treatment strategies (individual treatment, intensified disease management, targeted mass drug administration, community mass drug administration).

Thirdly, we also did not collect primary local data for utility weights and cost inputs in this study. We lacked data on QALY values (e.g., using Filipino EQ5D5L) from actual Filipino patients with scabies in the Philippines. Thus, we simply obtained DALY utility weights from the Global Burden of Disease 2019.[55] It is noted that the IHME did not have any data source cited from the Philippines and were likely to have just estimated the figures from other countries with similar socioeconomic status. The mathematical approach we used for combining hypothetical DALYs was based on the suggested formulas and thus, we conducted scenario analysis using the different methods.[56] Our price assumptions were based on local drugstore and drug price reference index and may not reflect actual usage (i.e., senior citizen discounts or promotional discounts; as-needed intake of oral antihistamine). We simply based other non-drug costs (laundry, transportation, wages) on average market prices, and may not reflect variation in use. Lastly, the possibility of dropouts after the first dose of either ivermectin or permethrin was not considered as we assumed that they would complete the two-dose regimen. Other assumptions based on either expert opinion or statistical data were age-specific prevalence, bacterial co-infection rate, proportion of cutaneous/systemic adverse events, household size and age structure; these may be better modelled by using actual patient data from primary studies.

The WHO included scabies as an additional indication for oral ivermectin in its essential medicine list in July 2019, noting that it is effective and safe. Despite lacking cost-effectiveness analysis studies, the WHO noted that ivermectin is likely to result in cost savings when used by member countries. A framework drafted by the expert panel convened by WHO in 2019 recommended oral ivermectin-based (two-dose) mass drug administration for endemic communities with prevalence of scabies exceeding 10%.[59] It recommended intensified disease management (treatment of index case and close contacts) in areas with lower scabies prevalence (>2 to <10%) and essentially leaves it up to local health officials to consider contextual factors in choosing which strategy to implement. Although there are previous RCTs that computed the treatment cost per patient cured, no full economic evaluation has been done for scabies. To the best of our knowledge, this is the first study to estimate the costs and health outcomes of oral ivermectin, alone or in combination, vs permethrin, in the Philippines and the world. With the upcoming target in the WHO Roadmap to End NTDs to include scabies treatment in universal health care package by 2030, there is a need for oral ivermectin to be registered for the indication of scabies by the Philippine FDA. Only then can evidence on cost-effectiveness may be used by the Philippine Health Technology Assessment (HTA) Unit to decide if it is appropriate to include ivermectin in the PNF.[60] Study results can be used to inform clinical practice, guideline development, coverage decisions as well as public health control programs to provide effective but affordable scabies treatment for patients and communities.

CONCLUSION AND RECOMMENDATIONS

Using the patient perspective, both oral ivermectin (2-dose) and combination oral ivermectin/permethrin (single dose) seem to be cost-saving compared to permethrin. However, caution is advised in interpreting the results due to uncertainty and lack of primary and local epidemiological, clinical, and cost data as inputs to the decision tree model. Future well-designed, double-dummy, and adequately sized RCTs should determine comparative efficacy and safety of oral ivermectin and combination treatment with permethrin for scabies in Filipino patients, measuring itch relief, use of adjunctive anti-itch medications and QALYs in both children and adults. Future economic evaluation models can be further refined by including itch relief, compliance, costs, QALYs based on primary data from local studies.

The government can undertake budget impact analysis and value of information analysis, as appropriate, for coverage decisions and public health programs.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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APPENDICES

Appendix 1

Table A1.1. Assumptions for economic evaluation model and parameters

Variable	Dosage	Reference
Body Weight	Children: 16-18 y/o: 59 + 51.5 = 110.20/2 = 55.2 kg 15 kg + 55.25 kg = 70.25/2 = 35.125 = ~ 35 kg Average weight: 35 kg Adults: 60.5 + 52.5 = 113/2 = 56.50 = ~ 57 kg Average weight: 57 kg	https://www.fnri.dost.gov.ph/images/images/news/PDRI-2018.pdf
Age Structure for Index Case (based on prevalence in PDS-HIS)	Patients with scabies among new cases consulting at PDS institutions: 5 to 18 y/o = 37% 19 y/o and older = 63%	PDS-HIS 2010 to 2021

Age Structure for Household Members	Age Distribution, Philippines (Projected, PSA 2020)
	• Total Population: 109,947,900
	  • 0-4 y/o: 11,475,800 (10%)
	  • 5-19 y/o: 32,043,900 (29%)
	  • 20 y/o and older: 66,428,200 (61%)
	• Population >5 y/o: 98,472,100
	  • 5-19 y/o: 32,043,900/98,472,100 = 33%
	  • >20 y/o: 66,428,200/ 98,472,100 = 67%
		https://psa.gov.ph/sites/default/files/attachments/hsd/pressrelease/Table%201_0.pdf

Direct Medical Cost		
Oral IVM 200 ug/kg (2 doses, 1 week apart)	Children: 200 ug/kg x 35 kg = 7 mg = ~ ½ of 12 mg tab x 2 doses = 1 tablet 12mg/tab Adults: 57 kg x 200 ug/kg = 11.4 mg = 1 tab 12 mg/tab x 2 doses (1 week apart)	https://www.cdc.gov/parasites/scabies/health_professionals/meds.html
Combination Oral IVM + Topical Permethrin (1 dose of each, 1 week apart)	Children: IVM 12 mg (1/2 tab) + Permethrin lotion (1/4 bottle = 15 ml) Adults: IVM 12 mg (1 tab) + Permethrin lotion (1 bottle 30 ml)	https://www.cdc.gov/parasites/scabies/health_professionals/meds.html
Topical Permethrin 5% lotion 60 ml	Children: 15 ml/whole body application x 2 doses (1 week apart) = 30 ml / 60 ml bottle = ½ bottle Adults: 30 ml/whole body application x 2 doses (1 week apart) = 60 ml / 60 ml bottle = 1 bottle	https://www.mims.com/philippines/drug/info/permethrin?mtype=generic
Diphenhydramine (Itch)	Children: 1 mg/kg/dose x 35 kg = 35 mg/12.5 mg/5 ml = 2.8 x 5 ml = 14 ml x 14 days = 196 ml/60 ml bottle = 3.27 bottles Adults: 50 mg 1 tab at bedtime x 2 wks. = 14 tabs	https://www.pdr.net/drug-summary/Diphenhydramine-Hydrochloride%E2%80%93diphenhydramine-hydrochloride-1140#:~:text=1%20to%201.5%20mg%2Fkg,4%20times%20daily%20as%20needed.
Topical steroid (for contact dermatitis)	Children: Betamethasone cream 0.1% 5 g tube (5 mg / 5 g cream) 4 areas affected x 0.5 g/dose = 2 g 2x/day x 1 wk. = 28g/5g tube = 5.6 tubes Adults: Clobetasol propionate 500 mcg/g (0.05%) 15 g Topical Cream 1g 2x/day x 1 wk. x 4 areas affected = 56 g/15 g tube = 3.733 tubes	https://www.ncbi.nlm.nih.gov/books/NBK532940/

Table A1.1. Assumptions for economic evaluation model and parameters *(continued)*

Variable	Dosage	Reference
Paracetamol (Adverse event: Headache)	Children: 5 ml 4x/day x 2 days = 40 ml/60 ml bottle = 0.67 bottle Adults: 500 mg tab 1 tab 4x/day x 2 days = 8 tabs	https://www.mims.com/philippines/drug/info/paracetamol?mtype=generic
Cefalexin 500 mg (Superinfection, moderate)	Children ave. 35 kg x 37.5 mg/ kg = 1312.50 mg/3 doses = 437.50 mg/dose x 21 doses = 4 bottles of 250 mg/5 ml 60 ml syrup Adults: 500 mg cap 1 cap 3x/day x 7 days = 21 caps	https://www.mims.com/philippines/drug/info/cefalexin?mtype=generic

Cost of Permethrin/ Ivermectin for three household members (Prorated as one child, two adults)	• Population >5 y/o: 98,472,100
	  • 5-19 y/o: 33%
	  • >20 y/o: 67%
	  • Ratio of children to adults = ~ 1:2
		PSA 2020

Direct Nonmedical Cost		
Laundry	3 days' worth of clothes = 1 kg (1 shirt/1 denim pants) x 3 days = 3 kg 1 towel = 0.5 kg 1 bedding set = 1 kg Total weight per person = 4.5 kg Total weight for household of 4 persons = 4.5 x 4 = 18 kg No. of loads for 6 kg per load = 3 loads	Soak and Relax (Mabalacat, Pampanga) (https://soaknrelax.com/about/) PhP 45/kg x 18 kg = PhP 810 https://web.archive.org/web/20221007090236/https://soaknrelax.com/pricing/ Bubble Up (Makati, Metro Manila) (https://original-cl.com.ph/) PhP 35/kg x 18 kg = PhP 630 https://web.archive.org/web/20220817071813/https://original-cl.com.ph/pricing Suds (50 branches nationwide) PhP 44/kg x 18 kg = PhP 792 https://web.archive.org/web/20220701084907/https://suds.com.ph/services/
Transportation	Distance from health facility 6.36 km (0.668, 13.96) Jeepney fare: PhP 11 (1st 4 km) x 2 transfers x 2-way x 2 persons = PhP 88 LRT + 1 jeepney ride: PhP 30 + 11.00 (1st 4 km) = PhP 41 x 2-way x 2 persons = PhP 164 GRAB Car: (PhP 50 base + 18 PhP/km*7km) x 2-way = PhP 352 No need to multiply by 2 since GrabCar can have up to 4 passengers	 https://mb.com.ph/2022/10/4/ltfrb-only-30183-puvs-secure-new-fare-matrix-so-far https://www.lrta.gov.ph/tickets-and-fares/ https://newsinfo.inquirer.net/1612828/grab-seeks-p20-hike-in-base-fare#ixzz7YqD6SgkM
Indirect Nonmedical Cost		
Lost wages	NCR Daily Minimum Wage Rate (Non-Agriculture): 570/day x 2 days = PhP 1140 Region VIII Minimum Wage: 315/day x 2 days = PhP 630 Davao Region Minimum Wage (Agriculture): 438/day x 2 days = PhP 876	https://nwpc.dole.gov.ph/wp-content/uploads/2022/05/Latest-Wage-Orders-Matrix-as-of-08-June-2022.pdf

IVM, Ivermectin; PDS HIS, Philippine Dermatological Society-Health Information System; PSA, Philippine Statistics Authority; NCR, National Capital Region.

Table A1.2. Formulas for the terminal nodes of the Decision Tree Model

1st chance node	2nd chance node	Formulas
Ivermectin branch		
CureIVM *BCA* =pCurePerm*rCureIVM) *Scenario analysis for varying compliance* =pCurePerm*rCureIVM*0.95)	IVMWithAE	Costs=cIVM+cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages+cIVMHH+O4*((pIVMCutAE*cDermatitis)+(pIVMSystAE*cHeadache)) DALYs=((1-((1-DALY_Cure)*(1-DALY_Headache))))/52
	IVMNoAE	Costs=cIVM+cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages+cIVMHH DALYs=DALY_Cure
Fail IVM (=1-CureIVM)	IVMWithAE	BCA Costs=1.5*cIVM+2*(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+1.5*cIVMHH+pBactInf*cBactInf+O20*((pIVMCutAE*cDermatitis)+(pIVMSystAE*cHeadache)) DALYs=1-((1-((DALY_Scabies/12)*0.95+(((1-(1-DALY_Scabies)*(1-DALY_BactInf))/12)*0.05))))*(1-((DALY_Headache)/52)) *Scenario analysis for Multiplicative approach for DALYs* DALYs= (DALY_Scabies/12)*0.95+(((1-(1-DALY_Scabies)*(1-DALY_BactInf))/12)*0.05 then choose higher vs "1-(1-DALY_Headache/52)*(1-DALY_Dermatitis/52)"
	IVMNoAE	Costs=1.5*cIVM+2*(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+1.5*cIVMHH+pBactInf*cBactInf DALYs=((DALY_Scabies/12)*0.95)+(((1-(1-DALY_Scabies)*(1-DALY_BactInf))/12)*0.05)
Permethrin branch		
CurePerm *BCA* =pCurePerm *Scenario analysis for varying compliance* =pCurePerm*0.70	PermWithAE	Cost=cPerm+(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+cPermHH+O36*((pPermCutAE*cDermatitis)+(pPermSystAE*cHeadache)) DALYs=((1-(1-DALY_Cure)*(1-DALY_Headache)))/52
	PermNoAE	Cost=cPerm+(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+cPermHH DALYs=DALY_Cure
FailPerm (=1-pCurePerm)	PermWithAE	BCA Cost=1.5*cPerm+2*(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+1.5*cPermHH+pBactInf*cBactInf+O52*((pPermCutAE*cDermatitis)+(pPermSystAE*cHeadache)) DALYs=1-((1-((DALY_Scabies/12)*0.95+(((1-(1-DALY_Scabies)*(1-DALY_BactInf))/12)*0.05))))*(1-((DALY_Headache)/52)) *Scenario analysis for Multiplicative approach for DALYs* DALYs= (DALY_Scabies/12)*0.95+(((1-(1-DALY_Scabies)*(1-DALY_BactInf))/12)*0.05 then choose higher vs "1-(1-DALY_Headache/52)*(1-DALY_Dermatitis/52)"
	PermNoAE	Cost=1.5*cPerm+2*(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+1.5*cPermHH+pBactInf*cBactInf DALYs=((DALY_Scabies/12)*0.95)+(((1-(1-DALY_Scabies)*(1-DALY_BactInf))/12)*0.05)

Table A1.2. Formulas for the terminal nodes of the Decision Tree Model *(continued)*

1st chance node	2nd chance node	Formulas
Combination treatment branch		
CureCombi *BCA* =pCurePerm*rCureCombi *Scenario analysis for varying compliance* =pCurePerm*rCureCombi*0.825	CombiWithAE	Cost=cCombi+(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+cCombiHH+O68*((pCombiCutAE*cDermatitis)+(pCombiSystAE*cHeadache)) DALYs=((1-(1-DALY_Cure)*(1-DALY_Headache)))/52
	CombiNoAE	Cost=cCombi+(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+cCombiHH DALYs=DALY_Cure
FailCombi (=1-pCureCombi)	CombiWithAE	*BCA* Cost=2*cCombi+2*(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+2*cCombiHH+pBactInf*cBactInf+O84*((pCombiCutAE*cDermatitis)+(pCombiSystAE*cHeadache)) DALYs=1-((1-((DALY_Scabies/12)*0.95+(((1-(1-DALY_Scabies)*(1-DALY_BactInf))/12)*0.05))))*(1-((DALY_Headache)/52)) *Scenario analysis for Multiplicative approach for DALYs* DALYs= (DALY_Scabies/12)*0.95+(((1-(1-DALY_Scabies)*(1-DALY_BactInf))/12)*0.05 then choose higher vs "1-(1-DALY_Headache/52)*(1-DALY_Dermatitis/52)"
	CombiNoAE	Cost=2*cCombi+2*(cDiphen+cTopSter+cPF+cLaundry+cTranspo+cLostWages)+2*cCombiHH+pBactInf*cBactInf DALYs=((DALY_Scabies/12)*0.95)+(((1-(1-DALY_Scabies)*(1-DALY_BactInf))/12)*0.05)

Appendix 2. Relative risks for cure and adverse events for oral ivermectin vs permethrin and combination treatment vs permethrin

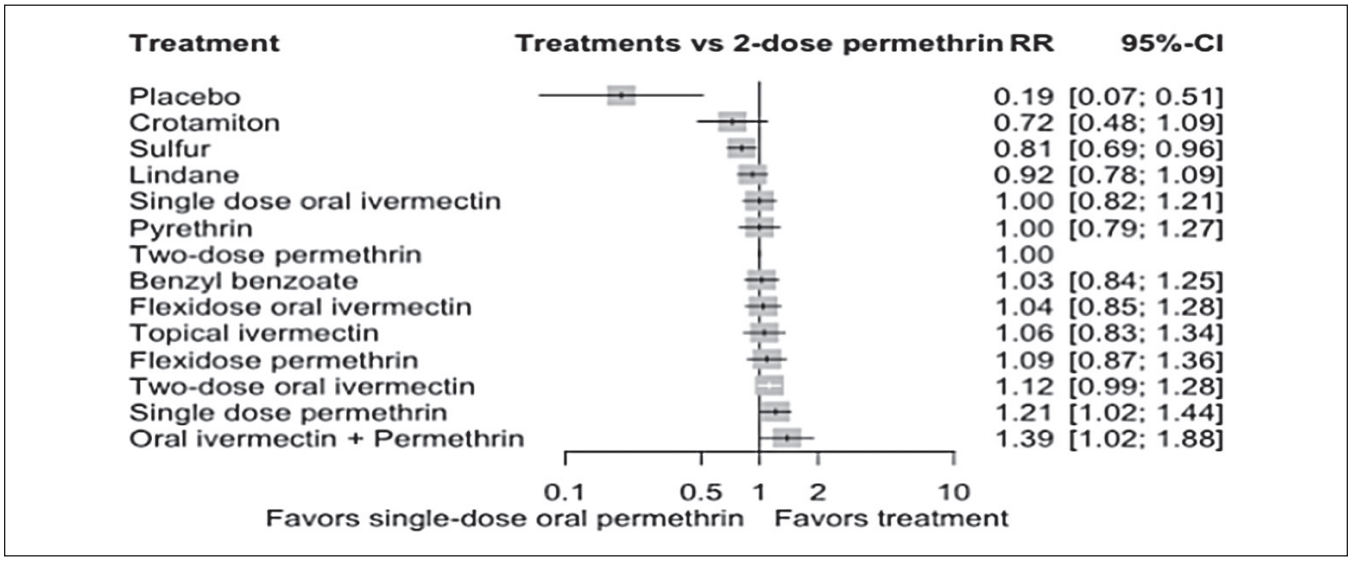


Figure A2.1. Interval plots for network sensitivity analysis splitting the oral ivermectin and permethrin nodes for clinical cure (1 to 2 weeks), all treatments versus two-dose permethrin; random effects.

(Data from Genuino et al., 2022).

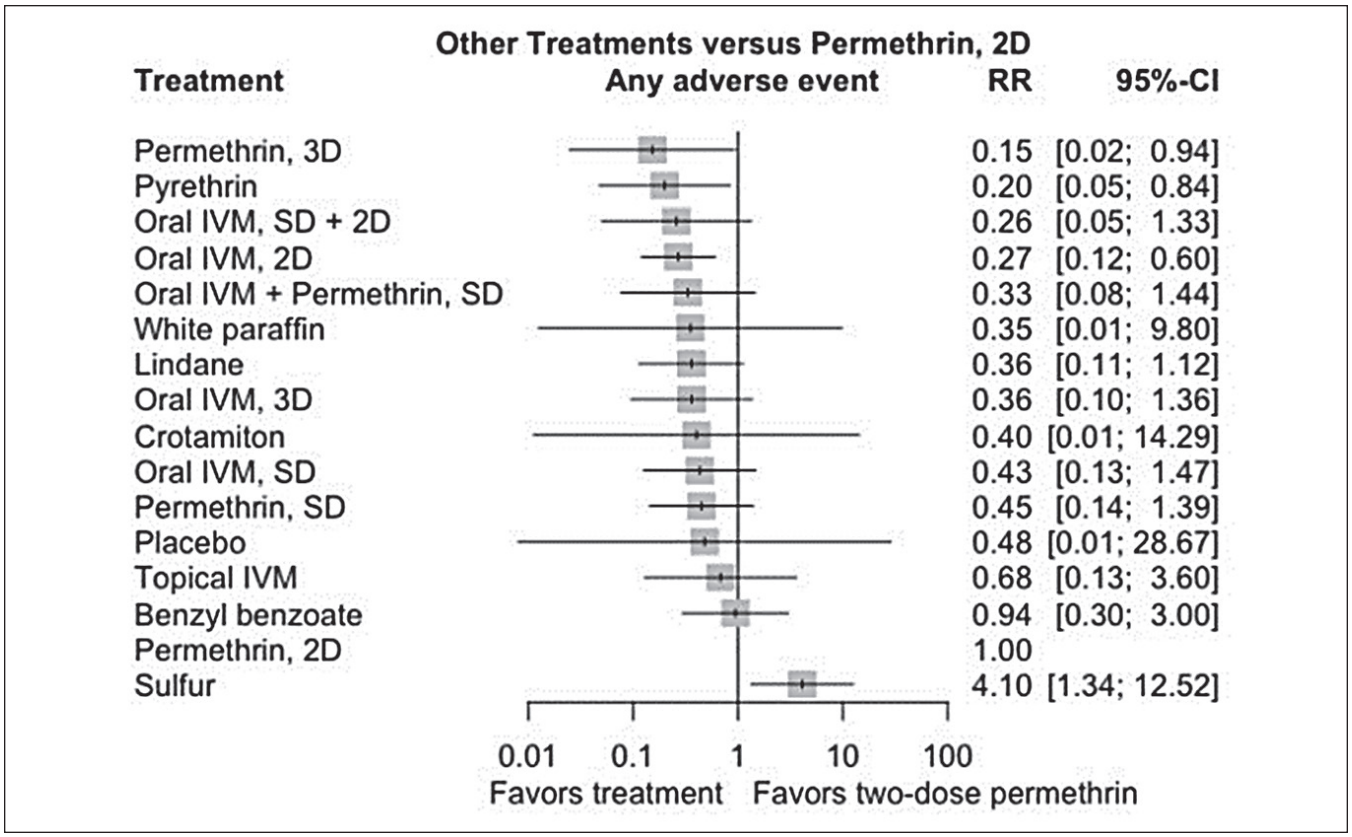


Figure A2.2. Interval plots for network sensitivity analysis splitting the oral ivermectin and permethrin nodes for adverse events (1 to 2 weeks), all treatments versus two-dose permethrin; random effects.

(Data from Genuino et al., 2022).

Appendix 3. Proportional meta-analysis of clinical outcome rates for permethrin

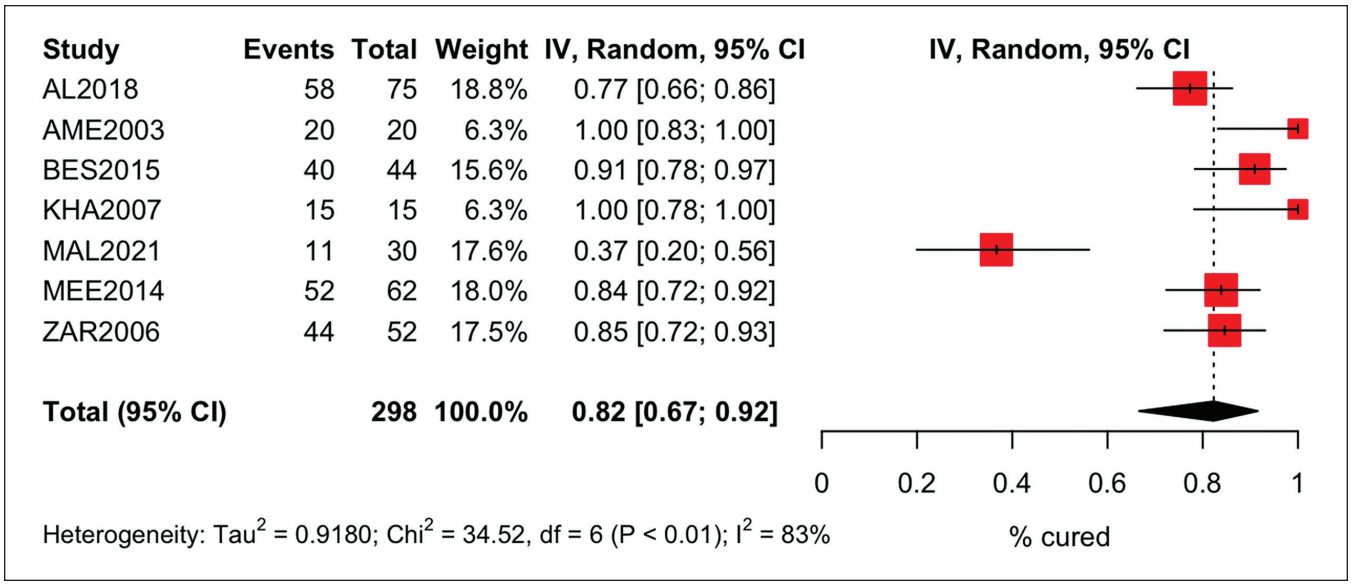


Figure A3.1. Proportional meta-analysis for permethrin (2-dose) cure rate at 1 to 2 weeks.

(Data from Genuino et al., 2022).

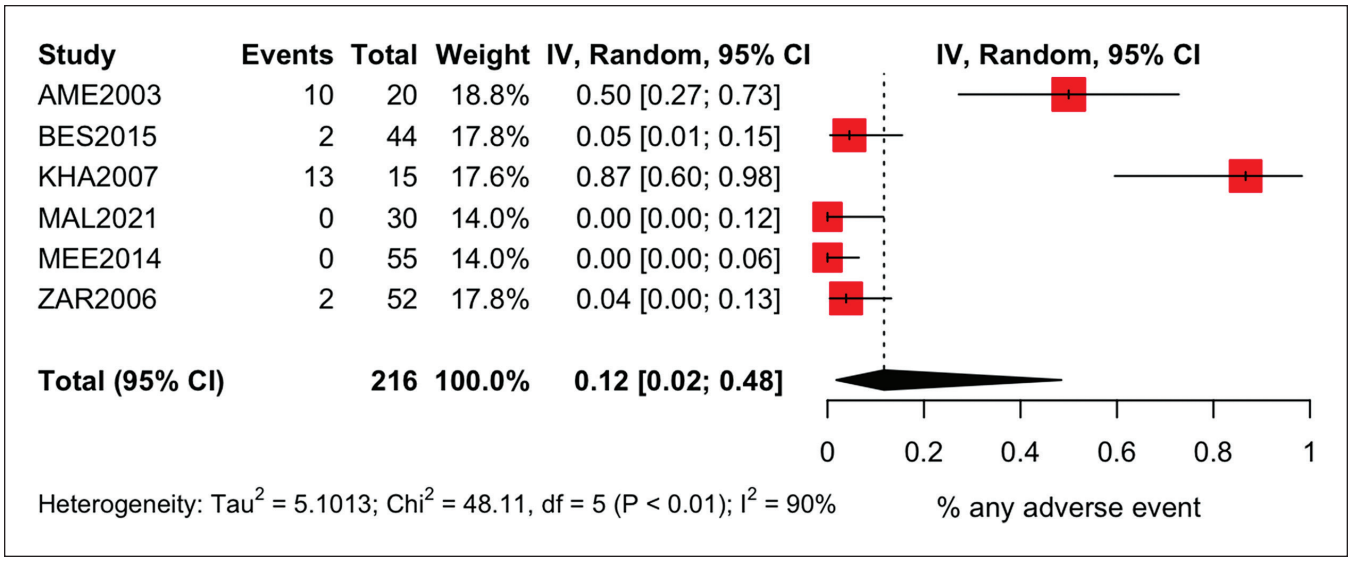
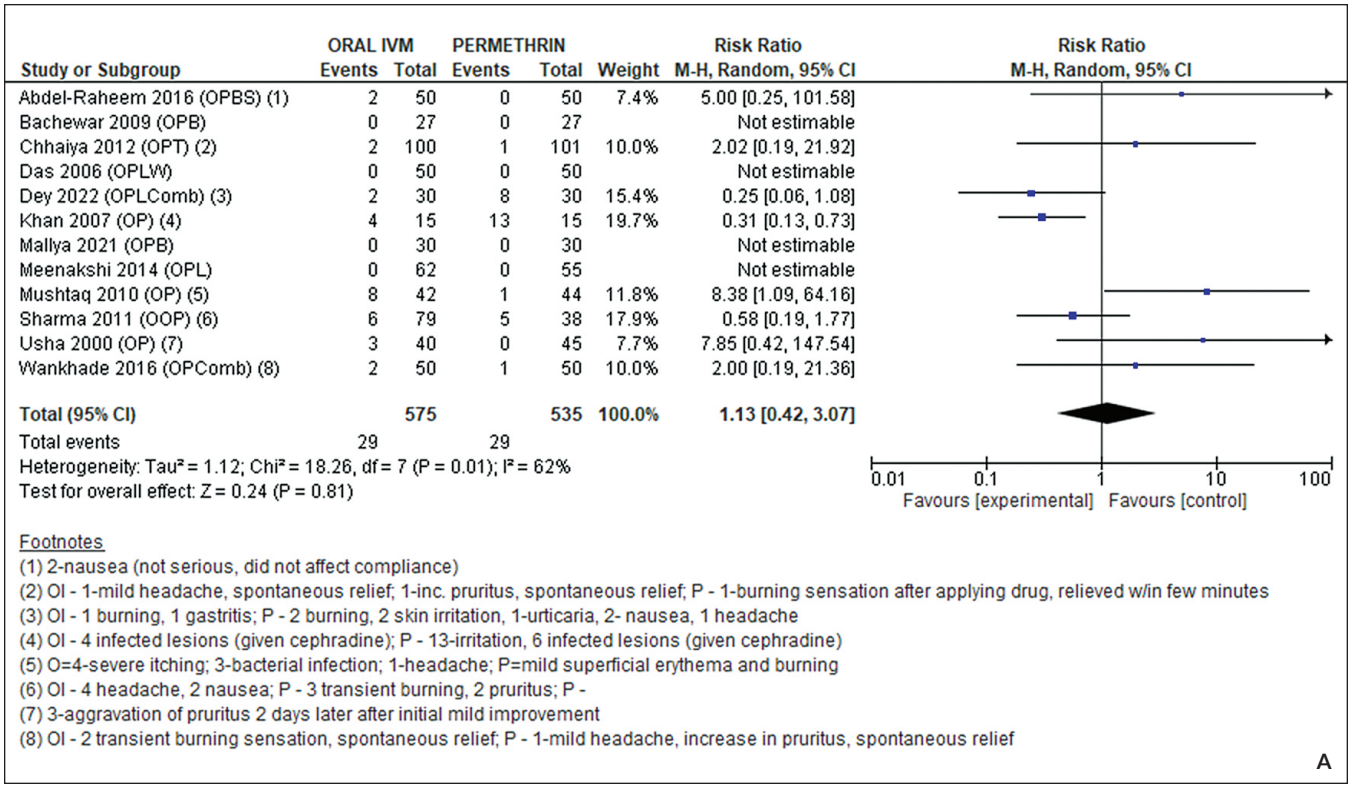


Figure A3.2. Proportional meta-analysis for permethrin (2-dose) adverse event rate.
(Data from Genuino et al., 2022).

Appendix 4. Forest plots from Pairwise/Network Meta-Analyses for Adverse Events (oral ivermectin vs permethrin; combination treatment vs permethrin)



Footnotes
(1) 2-nausea (not serious, did not affect compliance)
(2) OI - 1-mild headache, spontaneous relief; 1-inc. pruritus, spontaneous relief; P - 1-burning sensation after applying drug, relieved w/in few minutes
(3) OI - 1 burning, 1 gastritis; P - 2 burning, 2 skin irritation, 1-urticaria, 2- nausea, 1 headache
(4) OI - 4 infected lesions (given cephradine); P - 13-irritation, 6 infected lesions (given cephradine)
(5) O=4-severe itching; 3-bacterial infection; 1-headache; P=mild superficial erythema and burning
(6) OI - 4 headache, 2 nausea; P - 3 transient burning, 2 pruritus; P -
(7) 3-aggravation of pruritus 2 days later after initial mild improvement
(8) OI - 2 transient burning sensation, spontaneous relief; P - 1-mild headache, increase in pruritus, spontaneous relief

A

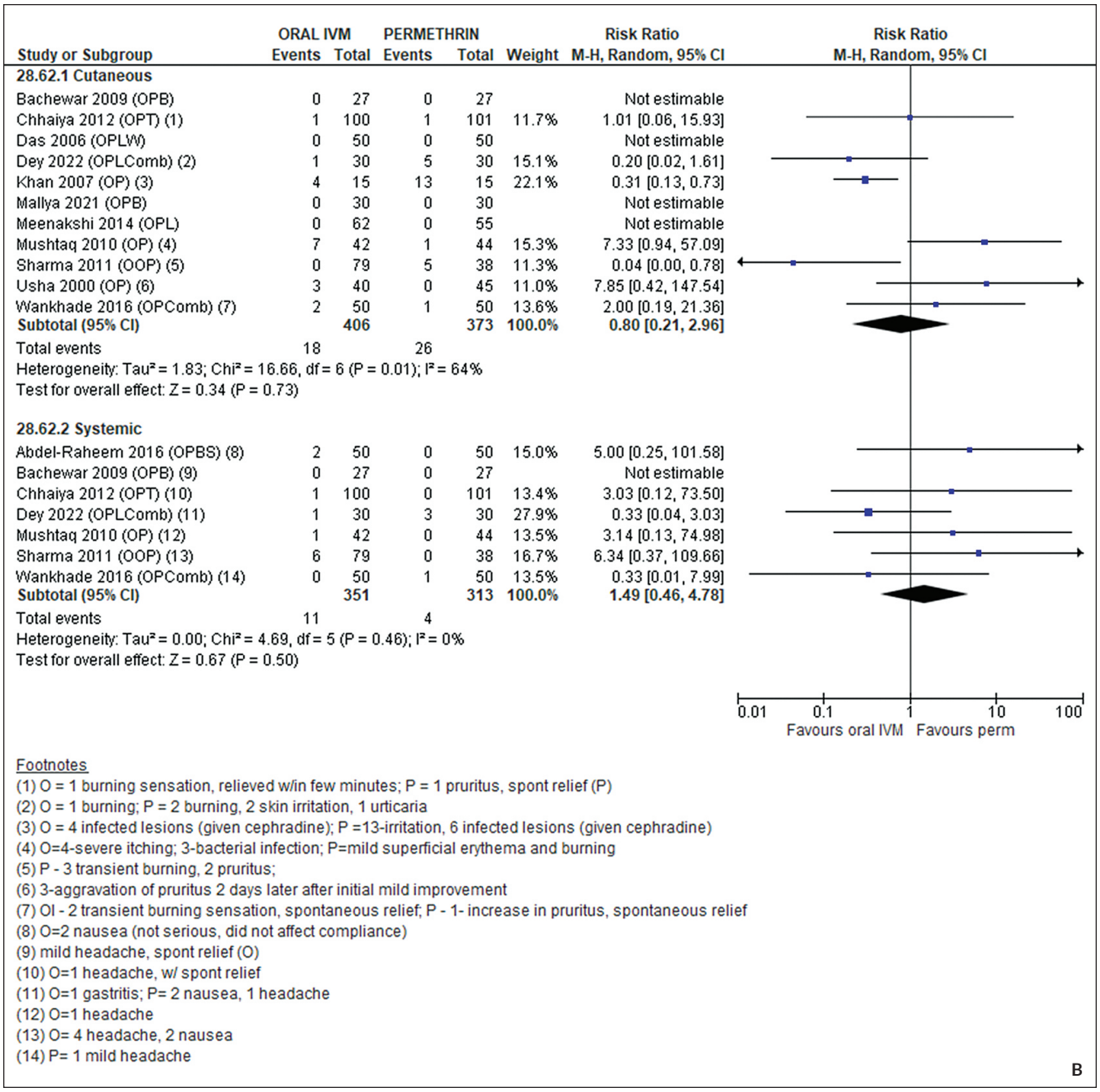


Figure A4.1. Pairwise meta-analysis for adverse events for oral ivermectin vs permethrin **(A)** main analysis, **(B)** subgroup by type of adverse event (cutaneous vs systemic).

(Data from Genuino et al., 2022).

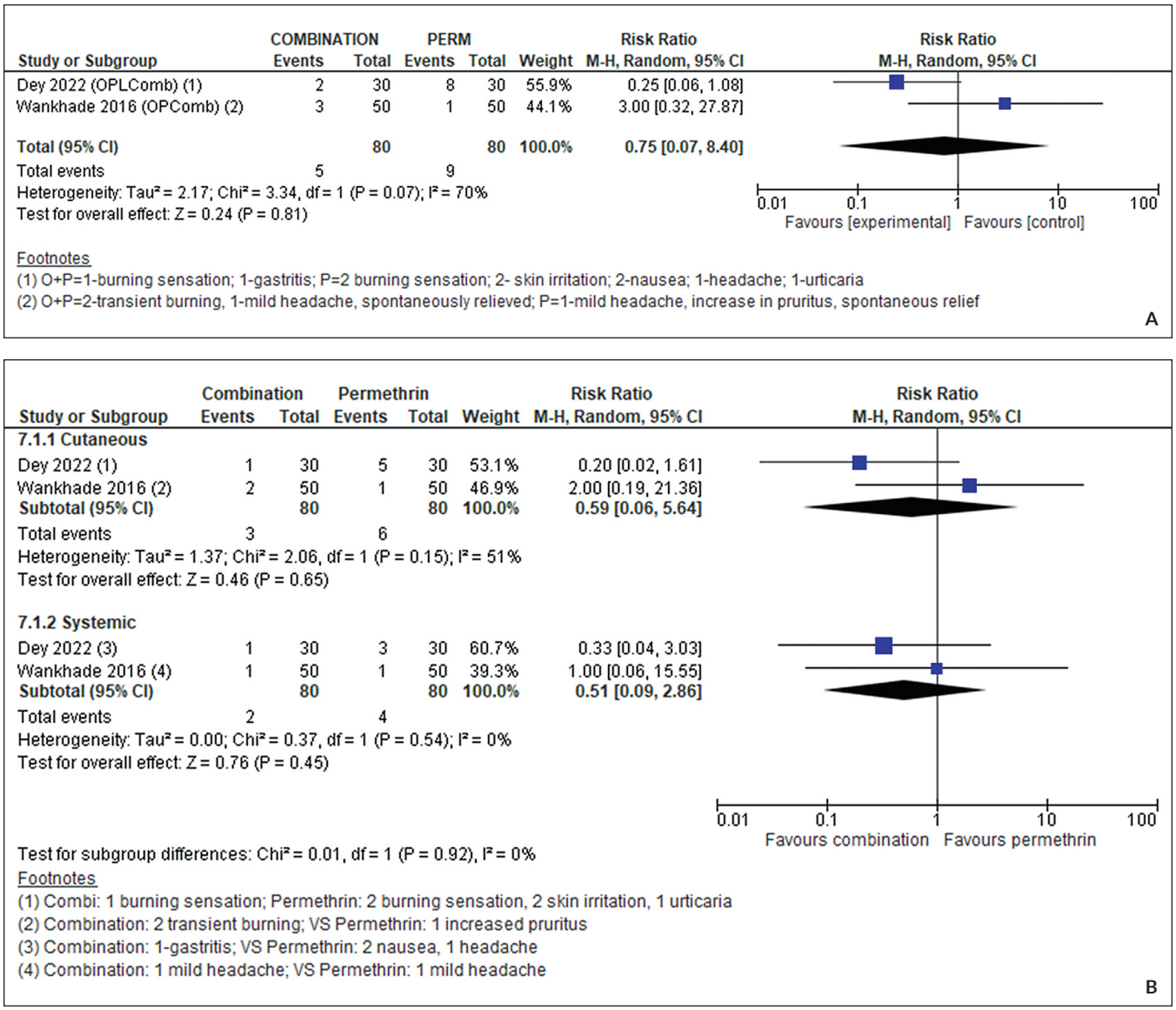


Figure A4.2. Pairwise meta-analysis for adverse events for combination vs permethrin **(A)** main analysis, **(B)** with subgroup by type of adverse event (cutaneous vs systemic).

(Data from Genuino et al., 2022).