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Physician acceptability of oral ivermectin versus permethrin in scabies treatment

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ABSTRACT

Oral ivermectin may be a cheaper and more convenient alternative to topical permethrin for classic scabies but its acceptability among physicians in the Philippines is underexplored. This qualitative study aimed to investigate physicians' experiences and perceptions regarding oral ivermectin, alone or in combination with permethrin, and only permethrin in the treatment of classic scabies. We interviewed 15 purposively sampled Filipino physicians: nine have prescribed only permethrin, one has prescribed either oral ivermectin or permethrin alone, and five have prescribed all three regimens for scabies. Interview data were analyzed and thematically organized using the theoretical framework of acceptability (TFA). Our findings reveal mixed awareness and experience with ivermectin among Filipino physicians: while most were generally confident in permethrin as the standard care, combination therapy was reserved as a last resort. These insights highlight the need for ongoing education, clearer guidelines, and further research to improve the efficacy and accessibility of scabies treatments while addressing physicians' varying perceptions and self-efficacy in alternative treatments.

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1. INTRODUCTION

Scabies, a highly infectious parasitic skin infestation, is a global public health issue that significantly impacts health and quality of life, poses an economic burden, and perpetuates poverty in resource-poor countries like the Philippines. Oral ivermectin is recommended as an alternative first-line agent to topical neurotoxic scabicides such as permethrin or phenothrin by the United States Centers for Disease Control-Sexually Transmitted Infections (US CDC-STI) [1], European [2], and Japanese scabies guidelines [3]. However, in the Philippines, interim guidance from the Department of Health (DOH) states that the use of oral ivermectin is off-label and may be considered for those with treatment failure or contraindication with topical permethrin, immunocompromise or crusted scabies, or outbreaks in closed settings where there are logistical

difficulties with topical treatment [4]. It is not recommended for pregnant women and children below 15 kg. Ivermectin was registered with the Philippine Food and Drug Administration in May 2021 to treat human nematode infections due to public demand during the COVID-19 pandemic [5] but it is not labelled for use in scabies. Despite the expiration of this registration in November 2022 [6], oral ivermectin has been recommended by the Philippine DOH for treating filariasis in 2021 [7].

Oral ivermectin may have comparable efficacy and safety to permethrin based on two previous systematic reviews [8], [9]. Both oral ivermectin and topical permethrin have few, mostly minor and transient adverse effects. Patients given oral ivermectin have reported itching, secondary bacterial infections, as well as systemic side effects such as headache and nausea [8]. When combined with certain drugs or chemicals, ivermectin can lead to harmful drug interactions or toxic effects such as hematomas and encepalopathy [10]–[12]. The mechanisms may involve inhibition of clotting factors, cytochrome P450 3A4 metabolic enzyme or blood-brain barrier transporters like multidrug resistance 1 (MDR1), breast cancer resistance protein (BCRP), or multidrug resistance-associated protein (MRP), or the presence of gene variations of these proteins. Common reported adverse effects of permethrin are mostly limited to skin and include mild and transient itching, burning, stinging, numbness, tingling, rash, erythema, eczema, and localized edema [8], but a rare transient dystonic reaction was reported [13]. The combination of topical permethrin and oral ivermectin has been reported to cause transient burning sensation of the skin and mild headache [14], [15]. The acceptability of oral ivermectin among physicians in the Philippines is not well documented, although it may offer comparable efficacy and safety to permethrin [8], [9]. Topical permethrin alone (2-dose) (260 Php, 60 ml of 5% lotion) is more expensive than oral ivermectin alone (200 ug/kg; 2-dose) (44 Php, two 12-mg tablets). Combination regimen may be cheaper (152 Php for a single dose of oral ivermectin and topical permethrin) or more expensive (304 Php for two doses of each drug (leading Philippine drugstore, as of June 2023).

Understanding physicians' experiences and perceptions regarding scabies treatment options is crucial for improving patient outcomes and treatment adherence. Without this knowledge, it is difficult to address potential barriers to the adoption of oral ivermectin and to provide the necessary support for its use in clinical practice. This study aimed to explore the experiences and perceptions of a small selected group of Filipino physicians regarding the use of oral ivermectin, topical permethrin and their combination to treat scabies.

2. METHOD

2.1. Design

A qualitative study design using a constructivist/interpretivist paradigm was employed. We sought to understand the ‘meaning’ of physician experiences and perceptions underlying treatment acceptability. The study protocol was approved by the University of the Philippines Manila Research Ethics Board (UPM-REB) (2022-0055-01).

2.2. Setting and duration, and sampling

The study was conducted in the Philippines between October 2022 to January 2023. We used purposive and snowball sampling to recruit 15 to 20 Filipino primary care physicians and dermatologists with at least three years clinical experience in managing scabies and other skin neglected tropical diseases (NTDs), and who have prescribed either oral ivermectin, permethrin, or their combination for classic scabies. We invited physicians through three specialty societies and medical organizations: the Philippine Dermatological Society (PDS), the Philippine Academy of Family Physicians (PAFP), and the Association of Municipal Health Officers of the Philippines (AMHOP). We excluded physicians with a conflict of interest (i.e., financial, social, and research).

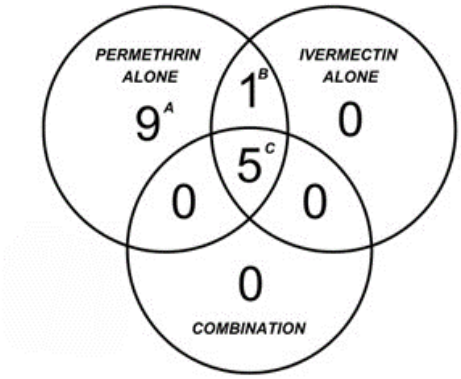
2.3. Sample

We interviewed 15 physicians: seven dermatologists, four family/community medicine, and four general practice. Median age was 46 years (range, 27 to 67) and median duration of practice was 16 years (range, 4 to 38). Majority were female (12/15), and practiced in the National Capital Region (NCR) (10/15). Overall, five physicians (dermatologists) prescribed all three regimens (P/I/C), one (family medicine) prescribed permethrin-alone and ivermectin-alone (P/I), while nine only prescribed permethrin-alone (P-only) (mixed specialties) as shown in Figure 1.

2.4. Data collection

We conducted one-time in-depth interviews using a validated and pretested semi-structured English interview guide [16], [17]. Content and face validity was ensured by an expert panel consisting of dermatologists with public health and epidemiology background. We also pretested the interview guide among the target study population prior to use. After obtaining written consent forms, physicians were interviewed virtually (through

Zoom) or face-to-face. The interviews were conducted by the primary investigator while a co-investigator or research assistant took down field notes. Interviews recordings were transcribed verbatim by trained research assistants, including nonverbal information such as vocal inflections, utterances, and gestures. Transcriptions were anonymized (i.e., labelled as P1 and P2) and confidentiality was ensured by storing personal information, recordings, and transcriptions in a secure storage. Transcripts were not returned to informants for comment and/or correction.



Note: A, Dermatologists; B, Family Medicine; C, General practitioners

Figure 1. Drugs prescribed by interviewed physician informants

2.5. Data analysis

We used the theoretical framework of acceptability (TFA) [18] to guide data analysis. The TFA was developed to assess the acceptability of healthcare interventions to users (e.g., patients) and providers (e.g., physician prescribers) [18]. The TFA theorizes that acceptability consists of seven domains: affective attitude, burden, ethicality, intervention coherence, opportunity cost, perceived effectiveness, and self-efficacy as presented in Table 1. In this study, we modified this framework by adding an eighth domain, accessibility, considering that healthcare services should be physically and financially accessible to patients [19], [20]. All these domains may affect the physician's decision-making and prescribing preference.

Table 1. Modified TFA

Domain	Definition
1 Affective attitude	Feelings about the intervention or drug.
2. Burden	Effort needed to prescribe the drug
3. Ethicality	How prescribing the drug fits with the physician's values
4. Intervention coherence	Understanding how the drug works
5. Opportunity cost	What the physician must give up in order to prescribe the drug
6. Perceived effectiveness	How well the drug is likely to work
7. Self-efficacy	Confidence in prescribing the drug
8. Accessibility*	Being affordable and easily available for purchase when prescribed

*Added domain

A reflexive iterative thematic analysis was followed [21], with the principal investigator-interviewer (RG) and a co-investigator (AM or MB) independently coding the data after reading them thoroughly, and regularly meeting to discuss and agree on codes. Codes were organized by domains of the modified TFA and later grouped into themes, using a deductive-inductive approach. The predominant themes for each prescribed drug and their most representative quotes were identified. Trustworthiness and credibility were ensured by memoing, bracketing, and keeping an audit trail [22].

3. RESULTS AND DISCUSSION

There were three predominant themes for each prescribed drug and are listed in Table 2. Ivermectin elicited mixed awareness and experience with its uses and safety but its prescribing practice seemed to be backed by evidence. The combination ivermectin and permethrin regimen was noted to have distinct advantages but still was viewed with some reservation. On the other hand, permethrin was perceived to be the standard of care despite issues with patient compliance.

Table 2. Predominant themes for each prescribed drug

Intervention	Predominant themes
Ivermectin	1. Mixed awareness and experience with ivermectin
	2. Mixed perceptions on ivermectin safety
	3. Evidence-based approach in prescribing ivermectin
Combination ivermectin/Permethrin	1. Combination treatment generally reserved as last option
	2. Combination treatment ensures fast and adequate cure
	3. Combination treatment provides multi-faceted advantages
Permethrin	1. Confidence in prescribing permethrin as standard of care
	2. Difficulty in ensuring patient compliance with permethrin
	3. Perceived efficacy of permethrin

3.1. Ivermectin

3.1.1. Mixed awareness and experience with ivermectin

Two of six ivermectin prescribers noted that among colleagues, ivermectin was rarely prescribed and with reservations:

> *"There were not a lot of dermatologists using it. So, I [thought] might find* myself *in hot waters if [I prescribe it]."* (P4, 67/F, dermatologist)

One non-prescriber just opted to stick with what's *'in the book'* since she was not able to confer with other physicians on their experience with ivermectin in their patients with scabies (P8, 27/F, general practitioner, P-only). Seven non-prescribers, despite becoming aware of it due to the COVID-19 pandemic (2/7) and from medical training (3/7), were unfamiliar with ivermectin's oral preparation for humans, availability, and indication and dosing for scabies. One non-prescriber was curious about ivermectin but wanted to study it more:

> *"Only when I know more about ivermectin will I prescribe it."* (P9, 42/F, family medicine)

One other non-prescriber would prefer to give ivermectin first to adults since he may make mistakes in pediatric dosing: One non-prescriber feared:

> *"Doing more harm than good"* since she was not confident with self-research. (P8, 27/F, general practitioner)

3.1.2. Mixed perceptions on ivermectin safety

Four out of six prescribers considered ivermectin safe. Two prescribers highlighted its established safety in mass drug administration for scabies and other parasitic diseases. P1 remarked:

> *"Look at all the literature. It's really been given what, for the past 50 years, given worldwide, over 50 million people in Africa... minimal side effects, minimal ADRs. No renal complications, no hepatic complications."* (P1, 50/F, dermatologist)

For three prescribers, their patients experienced either no side effects or only mild ones. One prescriber even expressed that she was:

> *"Confident enough [that ivermectin] is not going to hurt [patients]"* even with repeat doses. (P10, 54/F, dermatologist)

She stressed that smaller doses were given for scabies, unlike for COVID-19. However, five prescribers expressed caution about self-medication:

> *"[Ivermectin] may be abused. People might think since it's only one dose, they can self-medicate...It's scary because with COVID, they can get ivermectin left and right."* (P14, 46/F, family medicine)

Two non-prescribers were concerned about severe neurological side effects due to the pandemic-induced media hype but acknowledged that they have not heard of deaths or serious effects due to ivermectin. In addition, one P-only prescriber was concerned with the irreversibility of systemic side effects:

> *"Because if you give something that's systemic, you can't take it back. Unlike with topical medication, where side effects are localized, you can just wash it off"* (P3, 67/F, dermatologist, P-only)

3.1.3. Evidence-based approach with ivermectin

Five prescribers justified the use of ivermectin due to its proven efficacy based on published literature in other countries and WHO-recommended use in mass drug administration. P15 (52/F, dermatologist), a prescriber, was confident that:

> *"This is not a controversial drug if used properly"* and is *"lifesaving in many parasitic conditions."*

However, 3 out of 5 prescribers still acknowledge the need for more evidence, food and drug administration approval, and formulary inclusion by Department of Health (DOH) to make ivermectin an accepted alternative for scabies treatment. On the other hand, even non-prescribers would seek more guidance from local practice guidelines, expert lectures, and endorsement by the DOH, colleagues, and the local dermatological society.

> *"To allay the fears of prescribing ivermectin."* (P8, 27/F, general practitioner)

3.2. Combination ivermectin/permethrin treatment

3.2.1. Combination treatment generally reserved as last option

Four out of five combination treatment prescribers were hesitant to give this regimen as first-line and reserved it for select patient populations or as a last option for treatment failure or recurrence after permethrin use. Two prescribers gave it as an alternative first-line treatment for those with difficulties with topical application and have poor quality of life, while three non-prescribers would consider giving it for severe scabies or *"technically difficult cases"* (P3, 67/F, dermatologist). Despite being a prescriber, P15 was uneasy using combination treatment as first-line, especially for new patients:

> *"You always go with standard of care. So, I would just give plain permethrin… And if they don't do well then we can talk about something like ivermectin."* (P15, 52/F, dermatologist)

Two non-prescribers and one prescriber were concerned with the additional expenses, yet no perceived significant increase in efficacy:

> *"If permethrin is 90–95% [effective], how much more is the combination? It's just added cost. [I'll give it for] hard to treat and technically difficult cases."* (P3, 67/F, dermatologist)

Additionally, one non-prescriber found it challenging that combination ivermectin/permethrin is a non-formulary medication:

> *"In the hospital, when we prescribe medications to our patients, when we want our patients to be covered by PhilHealth, the medication has to be within the prescription of Department of Health (DOH)"* (P9, 42/F, family medicine)

3.2.2. Combination treatment ensures fast and adequate cure

For three prescribers, combination treatment ensured fast and definite cure. The additional oral ivermectin in combination treatment was perceived by P6 (65/F, dermatologist), a prescriber, as worth the extra cost, especially:

> *"if you see a patient whose quality of life is so affected."* Even one non-prescriber shared that *"if I would want to remedy the problem faster, then I would do a combination of both topical and oral."* (P13, 45/F, family medicine)

3.2.3. Combination treatment provides multi-faceted advantages

Two prescribers espoused the potential advantages of combination treatment. One prescriber considered the benefits of complementary routes of administration and less risk of developing resistance:

> *"If they can't apply the permethrin [properly], taking ivermectin might make up for it... Maybe you should combine, less chance to develop resistance to permethrin. It seems like a two-drug combination, although I have no proof. I was thinking like how we treat leprosy or TB, right?*" (P10,

54/F, dermatologist). Even one non-prescriber would consider giving ivermectin in between two doses of permethrin *"to boost the effect."* (P2, 45/F, dermatologist)

3.3. Permethrin

3.3.1. Confidence in prescribing permethrin as standard of care

The majority of prescribers (13/15) expressed confidence with permethrin since it was standard of care. Seven permethrin prescribers were familiar with permethrin from medical training while four prescribers trusted the recommendations in textbooks, modules, and journal reports. Despite not being updated with the latest practice guidelines, one prescriber still relied on permethrin,

> *"That was how I was taught in Philippine General Hospital (PGH). Not sure if there are new guidelines but [permethrin] seems to work for me still."* (P10, 54/F, dermatologist)

One prescriber highlighted that it is a Philippine FDA-registered scabicide, while another prescriber considered permethrin his *"go-to treatment."* (P11, 32/M, general practitioner). Seven prescribers understood permethrin's unique ovicidal action:

> *"That's why it is a drug of choice compared to others, which are only for adult [mites]."* P6 (65/F, dermatologist).

3.3.2. Difficulty in ensuring patient compliance with permethrin

Ensuring compliance with permethrin was challenging for nine prescribers, necessitating strict follow-up measures for two prescribers. One prescriber resorted to scaring the patient about the risk of reinfestation if they were poorly compliant. Three prescribers found applying permethrin in large households burdensome, since it was costly and tedious. As P10, 54/F, dermatologist, noted:

> *"I don't really trust that patients ask all their household members to do the same."*

However, five prescribers found that patients were generally compliant with permethrin. Two of the five prescribers believed it was due to the ease of the *"one-day approach"* (P2, 45/F, dermatologist). Six prescribers found it necessary to provide detailed instructions for permethrin use. P8 (27/F, general practice) gave written instructions in the vernacular while P11 (32/M, general practitioner) gave a *"one-shot deal"* education for those in remote communities who were unlikely to follow-up. In addition, sourcing permethrin or explaining its proper use through detailed instructions interfered with clinic routines of three prescribers:

> *"It's a matter of explaining to your patient… If you only have five minutes for your patients, that's nothing. Goodbye. No. It's not enough."* (P6, 65/F, dermatologist). Eight out of 15 prescribers found permethrin generally not affordable, *"The challenge is if they can buy enough to cover the entirety of the body surface area"* (P11, 32/M, general practitioner), with two physicians concerned with possible skimping and poor adherence.

3.3.3. Perceived efficacy of permethrin

Majority of permethrin prescribers (12/15) considered permethrin highly effective in clearing skin lesions (3/12), with no or few treatment failures (7/12), with treatment failures usually attributed to misdiagnosis (2/12) since resistance was rare (1/12) (high perceived effectiveness). Other possible causes of treatment failure, according to 5/12 prescribers, are missed spots on application, poor compliance, and lack of environmental control.

Patients without follow-ups were regarded as cured according to 5/12 prescribers, rarely requiring second-line drugs. Prescribers advised patients that persistent itching was normal, and absence of new lesions was more important. P14 (46/F, family medicine) explained that patients highly regarded permethrin:

> *"I guess the patients can see… the response so I guess they feel that a 'wonder drug' was used on them [laughs] that is topical because most of them expect to drink it... but this is different, this is something that they apply."*

Seven prescribers understood permethrin's scabicidal action, correct dosing, and need for adjunctive treatment. P6 (65/F, dermatologist) recognized permethrin's unique ovicidal and larvicidal properties.

Ivermectin's efficacy, safety, track record (in neglected tropical disease (NTD) programs), and serendipitous availability (due to the COVID-19 pandemic) led to its use by a few physicians in our study in treating Filipino patients with scabies. These physicians had mixed awareness and familiarity with ivermectin and yet were open to an evidence-based approach. Combination ivermectin and permethrin treatment, despite fast and assured cure, was considered as a last option.

Variable awareness and familiarity with ivermectin suggest the overall lack of knowledge and experience in the use of ivermectin, alone or in combination with permethrin, in scabies. While oral ivermectin was included in the Philippine National Formulary (1993) and recommended for use in the DOH's lymphatic filariasis control program in 2021, the Philippine FDA warned "against the purchase and use of ivermectin veterinary products against COVID-19" [23]. The Philippine FDA further stated that the "registered ivermectin products in the country for human use are in topical formulations under prescription use only" for treating ectoparasites such as head lice and rosacea. In a similar vein, the PDS discouraged the use of oral ivermectin for COVID-19 [24]. While misinformation and controversy about oral ivermectin flourished, authorities could have emphasized its proven role in human parasitic diseases such as scabies, and NTDs [25]. Although oral ivermectin was later registered as an anti-nematodal by the Philippine FDA in mid-2021, its experimental use in COVID-19 initially required a compassionate special permit and a prescription from a physician that was compounded by a pharmacist [26]. Unfortunately, the emergency authorization for oral ivermectin expired in November 2022 and the drug was only available in a few Philippine drugstores as of September 2023.

Non-prescribers in our study cited the lack of local guidelines as their main reason for avoiding ivermectin. Evidence-based practice guidelines are considered by many as the highest form of evidence for decision-making [27], [28]. This is similar to Australian Aboriginal communities where all interviewed healthcare providers (HCPs) referred to the local guideline for the diagnosis and treatment of local skin infections [29]. A few months after our study ended, the DOH released the interim guidance on scabies stating the indications for off-label use of ivermectin; this may potentially change the prescribing practice of the non-prescribers in our study [4]. Future FDA approval of oral ivermectin for scabies would pave the way for its on-label use for scabies and may also encourage its rational use among physicians.

Most of the ivermectin prescribers in our study were dermatologists. Non-dermatologists may hesitate to prescribe oral ivermectin due to unfamiliarity and lack of FDA labelling. In contrast, off-label use is commonplace in dermatology practice and is considered a rational approach, given the diverse pathophysiology of skin disorders [30]. Some drugs remain off-label for skin conditions despite evidence on efficacy and safety due to the protracted process of clinical trials for new indications of previously approved drugs, which discourages marketing authorization holders in applying for new indications [31]. Consequently, mandating on-label use of drugs in guidelines or reimbursement schemes may limit effective treatment, especially for children and pregnant women [32], [33]. The development of local practice guidelines could facilitate the inclusion of scabies as a registered indication for oral ivermectin by the Philippine FDA, aligning with WHO recommendations [34]. Physician education, especially involving primary care physicians, will help promote the rational treatment of scabies as part of the universal health care program of the Philippines that ensures that all Filipinos are guaranteed equitable access to quality and affordable health care [35].

Combination treatment is used in other skin diseases such as acne, atopic dermatitis, and psoriasis to harness therapeutic synergy, potentially minimize adverse effects, and reduce the development of drug resistance [36]. However, physicians hesitate to prescribe combination without knowing the optimal dosing regimens or receiving recommendations for its use as a first line treatment for patients with classic scabies. Most prescribers in our study reserve this treatment for patients with severe scabies, poor quality of life, or a history of failed monotherapy. The Japanese scabies guidelines also suggested limiting its use only in classic scabies in immunocompromised individuals and elderly patients with intact liver function. It also recommended further study on the drug interactions, and efficacy and safety of the combination treatment with oral ivermectin and phenothrin [3]. Physicians in our study were also concerned about the added expense; combination oral ivermectin and permethrin (single dose of each drug) was the most expensive treatment and around five times costlier per one scabies case cured than a single dose of ivermectin, although only a little higher than a single dose of permethrin [15].

Permethrin was the most acceptable treatment prescribed by all physician informants in this study, despite the challenges in ensuring compliance. The reasons for the perceived poor compliance were cost, inconvenience of whole-body application, and difficulty in convincing asymptomatic contacts to undergo treatment. Considering that the average household out-of-pocket payment of Filipinos accounts for 41.5% of the health expenditure, permethrin may be unaffordable for most [37]. These experiences were also mirrored in an observational study of 40 households in two scabies-endemic Aboriginal communities in northern Australia with a community-based skin health program [38]. Although there was good adherence to topical permethrin treatment in 32/40 children (80%), most (247/440, 56%) household members, mostly males and asymptomatic individuals, did not comply with treatment. In another qualitative study in four remote Aboriginal communities with a scabies prevalence of 15%, potential barriers to permethrin use elicited from

parents/carers included confusion in proper application of cream, unpleasant smell and texture, the delay in healing of the skin infection after treatment, unwillingness of asymptomatic household members to apply the cream, and the fast turnover of household residents who move between houses [29]. Although all health care providers in this previous study have prescribed permethrin for children with scabies, they often prescribed localized "spot" treatment, and not whole-body application as stated in the local guideline. In addition, only a few advised treating the entire household due to the high cost and fast turnover of household members. Similarly, the use of permethrin cream for scabies was directed by nurses in a Fiji community to be applied on affected children only and rarely advised its simultaneous use on all close contacts [39]. Likewise, our study showed that physicians doubted whether patients followed medical advice and complied with the instructions and feared skimping due to budget constraints.

The strengths of this study include the diversity of informants (from both primary care providers and specialists), and the research team's unique combination of analytic expertise (dermatologist/clinical epidemiologist, dermatologist/public health/community medicine, general practitioner/psychology). Limitations included variable ivermectin availability, impacting physicians' ability to prescribe it and restricting participant recruitment. Our findings may be applicable only to countries where oral ivermectin is not approved for scabies, and scabies is not part of a national public health control program, or reimbursable in the national health insurance program.

4. CONCLUSION

This study has shown that selected Filipino physicians had mixed awareness and experience on ivermectin, reserved combination ivermectin/permethrin treatment as a last resort, and were generally confident with permethrin as standard of care for scabies treatment. There is a need for ongoing physician education, clear guidelines, and further research to enhance the efficacy and accessibility of scabies treatments while addressing physicians' varying perceptions and self-efficacy in utilizing these treatments. Our findings may be further verified among a bigger sample size of physicians, especially among those who have used ivermectin, alone or in combination with permethrin. Other stakeholders like public health program managers and patient support groups can also be interviewed to obtain a broader perspective on acceptability. Large-scale physician surveys may be conducted to gain more generalizable findings.

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