

Moxidectin as an Alternative Anthelmintic for *Strongyloides stercoralis*: A Systematic Review and Meta-Analysis

Authors: E. R. Yonatan^{1*}; L. F. J. Jusni¹; S. Alvianto¹; J. F. Taniadi¹; A. K. Sulaiman¹

Affiliations: ¹School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia.

ABSTRACT

INTRODUCTION: Strongyloidiasis, caused by *Strongyloides stercoralis*, is a significant health threat, especially in tropical regions. Ivermectin is the standard treatment, but concerns about resistance have spurred interest in alternatives like moxidectin, known for its favorable pharmacokinetics and potential efficacy.

METHODS: This systematic review and meta-analysis, registered with PROSPERO (CRD42024576472), evaluated randomized controlled trials on the efficacy and safety of moxidectin for *Strongyloides stercoralis* infections. PubMed, EBSCOHost, ProQuest, and Google Scholar were searched for relevant studies. Cure rates, mean larval reduction rates, and adverse events were analyzed, and study quality was assessed using the Cochrane Risk of Bias tool. Three trials with 1,062 participants were included in the analysis.

RESULTS: Moxidectin showed efficacy comparable to ivermectin (RR 0.98 [95% CI 0.95-1.01], I²=0%) and placebo, with cure rates meeting non-inferiority thresholds. Mean larvae reduction rates were high across studies, and adverse events were mild and infrequent, with headache as the most common. No serious AEs were reported, although the trials were underpowered to detect rare events.

CONCLUSION: Moxidectin provides a safe and effective alternative to ivermectin for treating strongyloidiasis, with advantages like a longer half-life and fixed dosing, particularly in limited-resource settings. However, further multicenter studies are necessary to validate these findings across broader populations.

Keywords: Moxidectin, Anthelmintic, *Strongyloides stercoralis*, Strongyloidiasis

INTRODUCTION

Strongyloidiasis is prevalent in subtropical and tropical regions. The Centers for Disease Control and Prevention (CDC) estimates that globally, 30 to 100 million people are affected by strongyloidiasis [1].

The recommended treatment for uncomplicated *Strongyloides* infections is oral ivermectin at a 200 µg/kg dosage for two days [2]. However, concerns have been raised about the potential development of resistance following repeated use of ivermectin, attributed to alterations in drug

***Corresponding author:** Eric Ricardo Yonatan. Tel: +6283892563919. Faculty of Medicine and Health Science, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia. Pluit Raya Street No. 2, North Jakarta, Indonesia, postal code 14440. Email: eric.yonatan@gmail.com; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Funding:** All authors: No funding was sought for this study; **Academic Integrity.** All authors confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE; **Ethics of human subject participation:** The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable; **Originality:** All authors: this manuscript is original has not been published elsewhere; **Review:** This manuscript was peer-reviewed by three reviewers in a double-blind review process; **Type-editor:** Claire (USA).

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receptors and metabolic pathways. An in vivo study investigating the mechanisms of ivermectin resistance highlighted the role of ATP-binding cassette (ABC) genes [3]. Additionally, follow-up research revealed that despite initial ivermectin treatment, larvae were detected in two-thirds of patients, further suggesting the emergence of drug resistance [4].

As ivermectin resistance increases, moxidectin is emerging as a potential alternative treatment for strongyloidiasis. Moxidectin is a semi-synthetic macrocyclic lactone anthelmintic effective against various parasitic infections in animals, including horses and dogs. In nematodes, it interacts with glutamate-gated chloride channels (GluCl), gamma-aminobutyric acid (GABA) receptors, and/or ABC transporters. This interaction enhances permeability, increasing chloride ions, hyperpolarization, and subsequent muscle paralysis [5]. Moxidectin has also been used in humans for the treatment of onchocerciasis. It is being considered for broader human use due to its advantageous pharmacokinetics and potential efficacy, including for strongyloidiasis, with some trials reporting promising results [6]. This systematic review and meta-analysis will evaluate the efficacy and safety of moxidectin in the treatment of *Strongyloides stercoralis* infection.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 statement guideline [7]. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42024576472.

Eligibility criteria

Types of Studies: This systematic review encompassed all published randomized controlled trials that assessed the efficacy and safety of moxidectin for treating strongyloidiasis. Studies outside this category, including reviews, observational studies, case reports, case series, conference abstracts, book chapters, commentaries/editorials, and research on non-human subjects, were excluded. Additionally, non-English articles and those without accessible full-text manuscripts were also excluded.

Participants: The patients included were adults or young adults diagnosed with *Strongyloides stercoralis* infection, confirmed through Baermann assays. Exclusion criteria applied to individuals with systemic illness (such as fever, anemia, or unmanaged severe chronic disease), conditions that might interfere with protocol adherence, or those who had received interfering drugs (warfarin or any anthelmintic medication) within four weeks prior to treatment. Patients who were pregnant, breastfeeding, or planning to become pregnant within three months post-treatment were also excluded.

Outcome of interest: This study's outcomes of interest were cure rate, mean larvae reduction rate, and adverse events reported.

Search Strategy

A comprehensive literature search was conducted across several electronic databases, including PubMed, EBSCO-Host, ProQuest, and Google Scholar, to identify eligible studies. Two independent authors carried out the search using the following keywords and MeSH terms: ("moxidectin" OR "milbemycin" OR "CL 301423") AND ("*Strongyloides stercoralis*" OR "Strongyloidiasis"). All retrieved studies were imported into EndNote reference manager software, where duplicates were removed before proceeding to title and abstract screening. The two reviewers independently assessed the studies in parallel, with agreement reviewed after each selection step, and a third reviewer resolved any discrepancies. The final selected studies underwent full-text review based on the predefined eligibility criteria.

Data Extraction

All included studies were analyzed, and the following data were extracted: first author, country of origin, study design, sample sizes, age, sex, inclusion criteria, administration protocol, and the outcome of interest. All authors performed the data extraction.

Risk of Bias Assessment

The quality assessment of the randomized studies was conducted using the Cochrane Collaboration's Risk of Bias tool for randomized

trials (RoB 2) [8]. This tool evaluates five domains: the randomization process, deviations from the intended intervention, missing outcome data, outcome measurement, and selection bias. The overall risk of bias was categorized as low, high, or having some concerns based on each domain. Two reviewers independently assessed each study, and disagreements were resolved through discussion with the entire review team until consensus was reached.

Statistical Analysis

Review Manager (RevMan) version 5.4 was used to extract and pool the data for quantitative synthesis. All patients were classified into two groups for comparison between the intervention

(moxidectin) and the control group. We analyzed the Cure Rate using relative risks (RR) and 95% CIs. The proportion data were compared using the Mantel-Haenszel method. A random effects model for the meta-analyses was used due to variations in how primary outcomes were reported or calculated across studies. Moxidectin's non-inferiority compared to control was determined from the lower bound of the pooled 95% CI combined analysis, which is above both the non-inferiority thresholds reported in included studies. Moxidectin's non-inferiority compared to control was assessed by evaluating whether the lower bound of the pooled 95% CI exceeded the non-inferiority (NI) margins defined in the included studies. The pooled analysis adopted the study-defined margins to respect the original

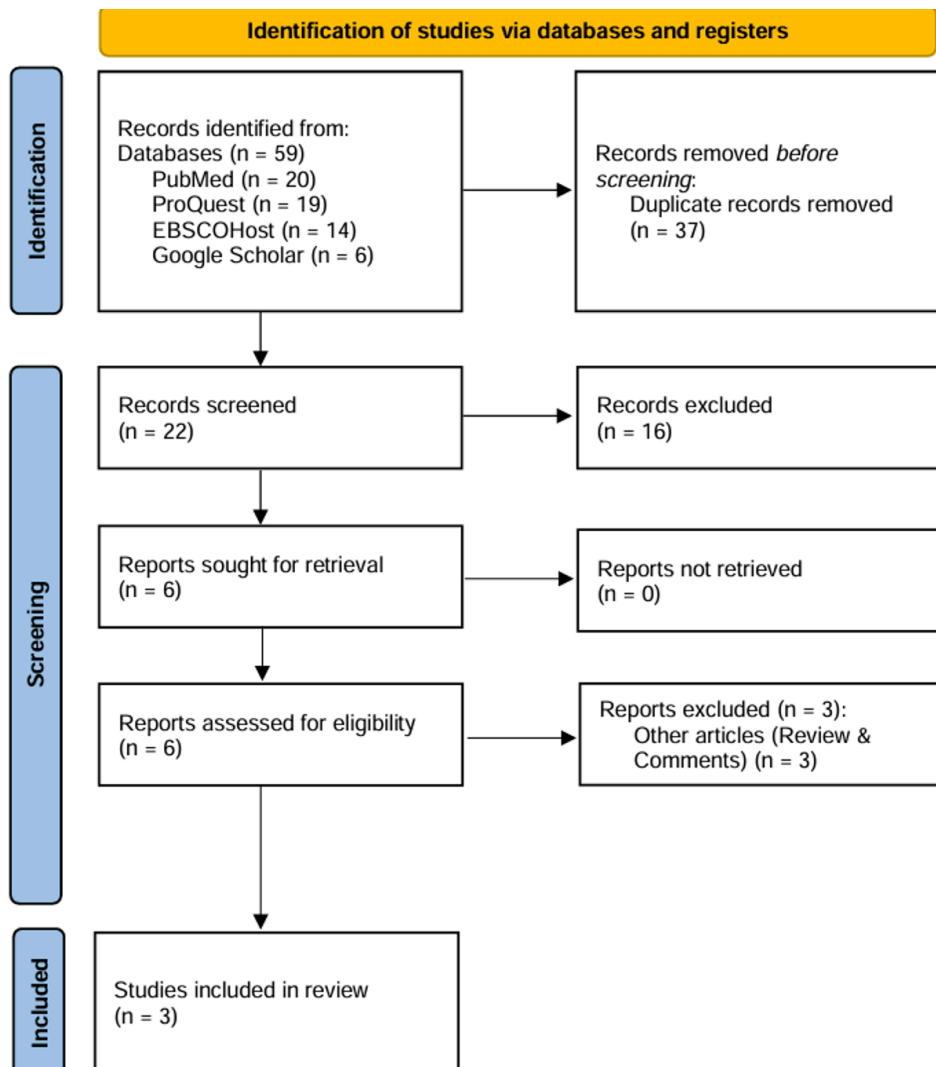


Figure 1: PRISMA 2020 Flow Diagram of Included Studies

clinical assumptions and trial contexts, which is consistent with other meta-analytical methods for synthesizing evidence across non-inferiority trials with differing thresholds.

Heterogeneity among trials was evaluated using the I² statistic. An I² value below 25% indicates low heterogeneity, values between 25% and 50% suggest moderate to substantial heterogeneity, and values above 50% indicate high heterogeneity [7]. A P value of less than 0.05 was considered statistically significant. Differences across studies were assessed based on sample sizes.

RESULTS

The study selection process and results were summarized in a flowchart, as shown in Figure 1. A total of 59 relevant studies were identified using the search strategy. According to the selection criteria, 22 were obtained after 37 studies excluded from the duplicate removal, and 6 were extracted after the title and abstract screening and were further identified for full-text screening based on the selection criteria. This process yielded 3 studies irrelevant to the criteria. Finally, three studies were included in the systematic review, and two of these studies met the requirements for data extraction and were incorporated into the meta-analysis.

Quality Assessment

The three studies evaluated using ROB-2 were generally found to have a low risk of bias, with some concerns on the first domains of the two studies due to concerns about the randomization process. In line with Cochrane’s recommendations,

the Robvis tool was used to summarize the bias risk (Figure 2), rated as “low,” “some concerns,” and “high” across all domains.

Characteristics of Included Studies

All three randomized controlled trials that met the inclusion criteria were included in this review, comprising 1,062 patients. Of these, 607 received moxidectin, while 455 were in the control group, with 29 patients receiving a placebo and 426 receiving ivermectin. Key study characteristics, including the number of participants, age, gender, inclusion criteria, administration methods, and outcomes of interest, were extracted and summarized in Table 1. The average age of participants was 44.14±12.02 years, and the study populations were predominantly male (54.7%) compared to female (45.3%). Two studies were conducted in Laos, and one was conducted in Laos and Cambodia.

Efficacy

Of the three studies reviewed, one by Hofmann et al. evaluated the efficacy and safety of moxidectin compared to a placebo for Strongyloides stercoralis infections. The results demonstrated that moxidectin provided promising efficacy in treating strongyloidiasis in adults, with doses ranging from 4 mg to 12 mg. The observed cure rates were between 83% and 90%, with efficacy increasing slightly with higher doses, leveling off at 8 mg. The study recommended an 8 mg dose as optimal for S. stercoralis infection, consistent with its use in other helminth infections (e.g., onchocerciasis).

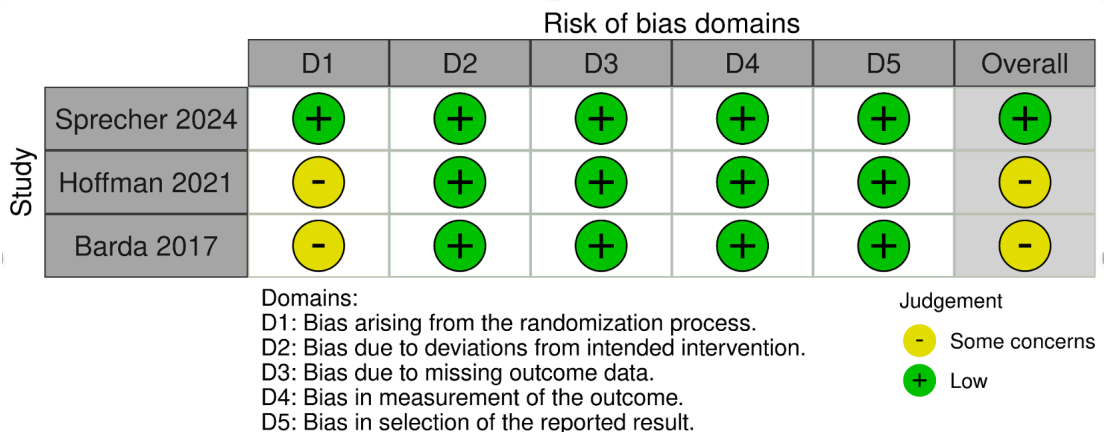


Figure 2: Results of Quality Assessment in RCT studies using RoB 2 tools

Table 2: Characteristics of included studies.

Study ID	Country	Design	Inclusion Criteria	Group	Participants			Duration	Most Common Adverse Events	Funding Sources
					Total (n)	Age (Mean, SD)	Male: Female			
Sprecher 2024[9]	Laos and Cambodia	Randomized, double-blind, parallel-group, phase 2b/3 trial	Participants aged 18-65 with <i>Strongyloides stercoralis</i> infection were tested using Baermann assays.	Moxidectin 8 mg orally once daily	363	Laos: 45.4 (11.6) Cambodia: 44.8 (12.8)	195: 168	14-21 days	Abdominal pain, headache	Swiss National Science Foundation
				Ivermectin (200 µg/kg body weight) single dose	363	Laos: 44.8 (11) Cambodia: 44.9 (12.7)	183: 180	days	headache	
Hofmann 2021[10]	Laos	Randomized, single-blind, parallel-group, placebo controlled, dose-ranging, phase 2a trial	Participants aged 18-65 with <i>Strongyloides stercoralis</i> infection were tested using Baermann assays.	Moxidectin orally divided by multiple doses (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg) single dose	180 (n=30, 29, 32, 29, 30, 30 per 2, 4, 6, 8, 10, 12 mg dose groups)	44.3 (11.86)	119: 61	28 days	Headache, diarrhea, itching	Fondazione Adiuware
				Placebo with the same procedure.	29	40.0 (10.7)	19: 10			
Barda 2017[11]	Laos	Randomized, single-blind, phase II trial	Participants aged 12-60 with <i>Strongyloides stercoralis</i> infection were tested using Baermann assays.	Moxidectin 8 mg orally once daily	64	39.4 (12.9)	31: 33	No	No participants reported any adverse events	European Research Council
				Ivermectin (200 µg/kg body weight) single dose	63	40.7 (10.9)	34: 29	21 days		

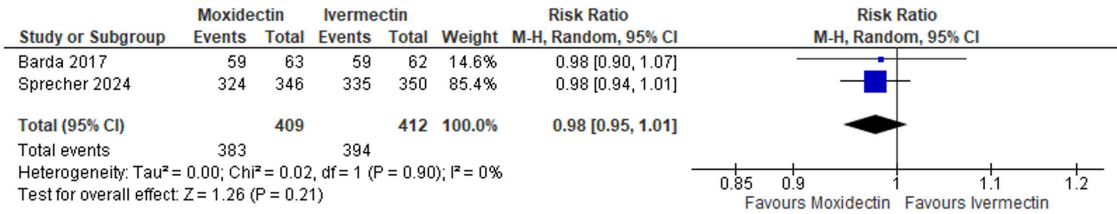


Figure 3: Forest Plot of Cure Rates in Strongyloidiasis Patients treated with Moxidectin versus Ivermectin

Two additional studies compared moxidectin (8 mg) to ivermectin (200 µg/kg) to treat *S. stercoralis* infection. Both studies found moxidectin to be an effective alternative to ivermectin. However, only one study demonstrated non-inferiority to ivermectin in terms of efficacy, based on the lower limit of the two-sided 95% confidence interval (CI) for the difference between treatments, which did not exceed the predefined non-inferiority margin. In a study by Sprecher et al., the cure rate was 93.6% (95% CI: 90.5%-96.0%) in the moxidectin group and 95.7% (95% CI: 93.0%-97.6%) in the ivermectin group, with a between-group difference of -2.1 percentage points (95% CI: -5.5 to 1.3), meeting the non-inferiority criterion with a margin of -10 percentage points. In Barda's 2017 study, cure rates were 93.7% for moxidectin and 95.2% for ivermectin. Non-inferiority requires a lower limit of 95% CI for the difference in cure rates not to exceed 7 percentage points. The difference was estimated at -1.5 percentage points (95% CI: -9.6 to 6.5), and since the lower limit exceeded the non-inferiority margin, non-inferiority was not conclusively demonstrated in this study.

The cure rates from the included studies were pooled and analyzed, as shown in Figure 3. The results indicated no significant difference between moxidectin and ivermectin for treating strongyloidiasis, with a relative risk (RR) of 0.98 (95% CI: 0.95-1.01). The heterogeneity test yielded an I² of 0%, suggesting no significant variation between the studies.

To further assess the non-inferiority of moxidectin, we combined the mean differences in cure rates between moxidectin and ivermectin across the studies, as illustrated in Figure 4. The combined mean difference was -2.01 percentage points (95% CI: -5.15 to 1.12). The lower limit of the 95% CI did not exceed the non-inferiority margins reported in the two studies (7 and 10 percentage points). Therefore, the pooled results confirmed that moxidectin was non-inferior to ivermectin in terms of cure rates for strongyloidiasis. The heterogeneity test again showed an I² of 0%, indicating no significant heterogeneity between the studies.

Studies reported high mean larvae reduction rates for moxidectin, with a study comparing moxidectin and placebo showing significantly greater reductions in the moxidectin group. The mean larvae reduction rate for moxidectin ranged from 97.8% to 99.8%, compared to 21.7% (95% CI, -67.1-51.9) for the placebo group. In the study by Sprecher et al., the moxidectin 8 mg group achieved a mean reduction rate of 99.5% (95% CI, 98.8–100), which was comparable to the ivermectin group, which reached 100% (95% CI, 100–100). Due to the absence of mean larvae reduction rate reports in the study by Barda et al., a quantitative analysis of the mean larvae reduction rate could not be performed.

While the meta-analysis compared moxidectin to ivermectin, Hofmann's placebo-controlled data

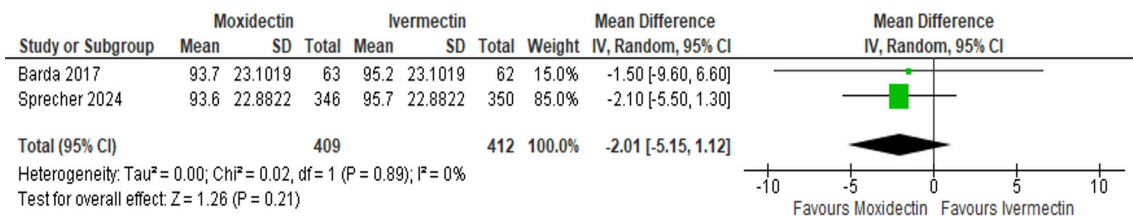


Figure 4. Forest Plot of Mean Differences in Cure Rates in Strongyloidiasis Patients treated with Moxidectin versus Ivermectin

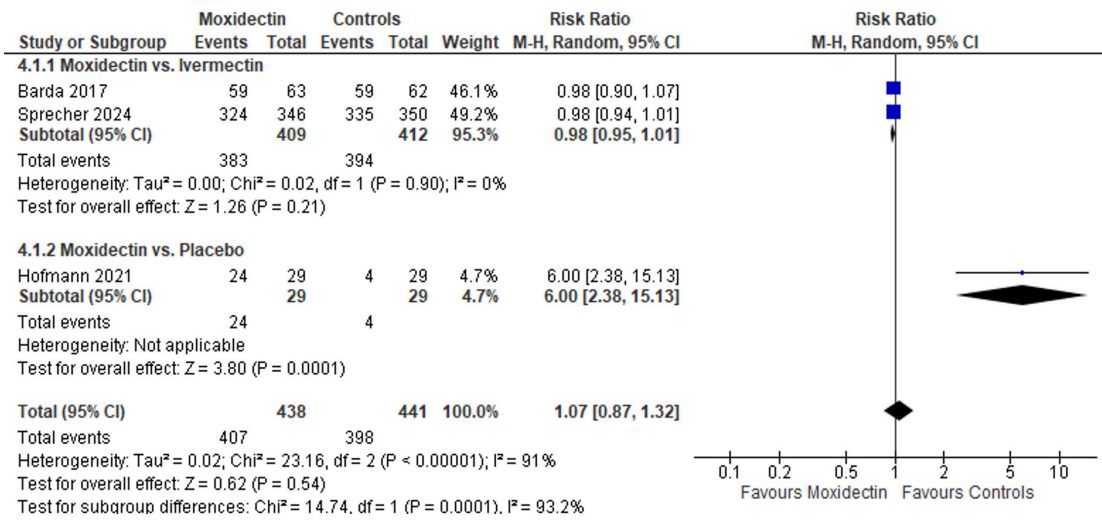


Figure 5: Subgroup analysis of Cure Rates in Strongyloidiasis Patients treated with Moxidectin versus Controls

were analyzed separately to preserve comparator consistency. In the following study, moxidectin demonstrated significantly higher cure rates compared to placebo (ranging from 83% to 90%), supporting its efficacy over no treatment. A subgroup analysis including placebo controls is presented in Figure 5 to illustrate these findings.

Safety

All three studies reported that moxidectin was well tolerated in patients with strongyloidiasis, with none of the participants experiencing significant side effects post-treatment. In the study by Barda et al., no adverse events were reported among the participants. The study by Hofmann et al., which compared moxidectin to a placebo, found that all reported symptoms were mild, with no serious adverse events across the investigated doses. The most common adverse events 28 days after treatment were headache (5%), diarrhea (2%), and itching (1%). In the recent study by Sprecher et al., adverse events were also predominantly mild and transient, with a safety profile comparable to ivermectin. The most frequently reported adverse events were abdominal pain (9% in both the moxidectin and ivermectin groups) and headache (7% in the moxidectin group vs. 8% in the ivermectin group). As no adverse events were reported in the study by Barda et al., a quantitative analysis of adverse events was not possible.

DISCUSSION

Strongyloides stercoralis infection is most prevalent in Southeast Asia, Africa, and the Western Pacific, accounting for 76.1% of global cases [12]. In Southeast Asia, endemicity is driven by warm, humid climates and socio-economic conditions that sustain transmission, with Cambodia and Laos having the highest prevalence in the region [13]. Higher infection rates are observed in males and rural children, likely due to increased exposure through outdoor activities and environmental factors [14].

Moxidectin is commonly used as an anthelmintic drug for animals such as dogs, cattle, and horses. In addition to treating Strongyloides stercoralis infection, moxidectin is also used to treat onchocerciasis [6]. In 2022, the WHO made a systematic review report about the effectiveness of moxidectin as a treatment for onchocerciasis in humans, thus indicating the potential of moxidectin as an anthelmintic drug for humans [15].

There is no significant difference in efficacy between moxidectin and ivermectin, as both show similar cure rates across three studies, with the combined mean difference remaining within the non-inferiority margins cited in two studies based on expert opinion. Additionally, studies reported that moxidectin has a high mean larvae reduction rate in patients with strongyloidiasis. Moxidectin and ivermectin are macrocyclic lactones that target glutamate-gated chloride ion channels, leading to hyperpolarization, paralysis, and parasite death. While moxidectin, a milbemycin,

is more lipophilic than ivermectin, an avermectin, the clinical significance of this difference remains unclear [16,17].

The study by Barda et al. could not demonstrate the noninferiority of moxidectin compared to ivermectin for *Strongyloides stercoralis* infections, whereas Sprecher et al. successfully established noninferiority. Several factors likely influence this outcome. Barda et al. had a smaller sample size, which reduced statistical power, a stricter noninferiority margin of 7 percentage points, and a more limited study scope, being an exploratory trial confined to a single region. In contrast, Sprecher 2024 employed a larger sample size, a broader noninferiority margin of 10 percentage points, and a rigorous multi-site, double-blind design across two countries, facilitating the successful demonstration of noninferiority [9,11].

Moxidectin is becoming a promising alternative for treating *Strongyloides stercoralis* infections, with notable benefits over traditional treatments like ivermectin. Administered as a standard 8 mg dose, moxidectin simplifies dosing protocols, particularly in community healthcare settings, by avoiding weight-based calculations required for ivermectin. This fixed-dose approach facilitates easier distribution among large groups [11,18]. After ingestion, moxidectin reaches peak blood levels within three to four hours and remains in the body for an extended period. With a half-life of 20–35 days, it may provide prolonged therapeutic effects and hold an advantage over ivermectin, which has a shorter half-life of 16–32 hours, especially for managing *S. stercoralis* auto-infections and potential re-infections. This extended presence could benefit individuals with *S. stercoralis* hyperinfection or disseminated infection due to immunosuppression [9,19]. Moreover, moxidectin offers additional benefits compared to ivermectin, including slower elimination, reduced neurotoxicity in preclinical studies, and effectiveness against certain ivermectin-resistant strains, positioning it as a promising option for future public health initiatives [18].

The US Food and Drug Administration authorized moxidectin in 2018 to treat onchocerciasis in patients 12 years of age and older [20]. It has been demonstrated that moxidectin has a lesser propensity for neurotoxicity than ivermectin [21]. In patients with strongyloidiasis, all three included studies reported that moxidectin was well tolerated, with none of the participants

reporting serious adverse events after treatments [9–11]. Phase 2a and 2b/3 trials confirmed its safety across various doses, with mild, temporary side effects like abdominal pain, headache, and diarrhea [9,10]. These findings align with studies from endemic regions, showing moxidectin's comparable safety to ivermectin in healthy volunteers [22]. Mazzotti reactions caused by rapid parasite death can occur within seven days post-treatment in strongyloidiasis patients co-infected with onchocerciasis [23]. Opoku et al. found similar reaction profiles for moxidectin and ivermectin, though severe Grade 4 reactions, including postural hypotension, were slightly more frequent with moxidectin. This hypotension resolved quickly with rest and occurred earlier than with ivermectin [22]. This shows that although common adverse events reported in this review were mild and transient, vigilance for hypotension in co-infected patients is warranted.

Evidence on the cost and accessibility of moxidectin for strongyloidiasis is limited, with a lack of clinical guidelines and underdeveloped supply chains hindering its adoption. While moxidectin is currently approved for onchocerciasis rather than strongyloidiasis, its supply chains and distribution systems for such off-label use are underdeveloped. Nevertheless, research by Turner et al. highlights that moxidectin-based approaches could accelerate the elimination of parasite transmission in onchocerciasis-endemic regions and reduce delivery costs compared to ivermectin-based programs, increasing interest in exploring alternative treatment strategies [24]. In 2024, efforts are instead concentrated on enhancing access to ivermectin, the standard treatment, as no endemic region currently has a dedicated public health program targeting strongyloidiasis. This includes initiatives like the WHO's push for affordable generic ivermectin prequalification and promotion of donation programs [25]. Despite moxidectin's promising efficacy and safety profile, its clinical adoption for strongyloidiasis remains limited by regulatory and logistical challenges. Currently, moxidectin is approved only for the treatment of onchocerciasis and has not received formal approval for strongyloidiasis, restricting its availability for off-label use. Additionally, supply chain limitations and a lack of established procurement pathways may hinder widespread implementation, particularly in low-resource settings.

Our systematic review thoroughly evaluates moxidectin's efficacy in patients with strongyloidiasis, emphasizing cure rates and examining the safety profile based on reported adverse events. This approach enables a more detailed analysis of the treatment's overall impact. Several limitations should be acknowledged in this review. The number and quality of included studies were limited, which may impact the robustness of our conclusions. Due to the scarcity of studies and limited data, a quantitative analysis of the mean larvae reduction rate and safety profile could not be performed. Another limitation of this review is the exclusion of non-English language studies. However, no relevant non-English articles were identified during the manual hand search. Additionally, the lack of multicenter studies is concerning, as all included studies were conducted in Laos, with one in Cambodia, potentially restricting the generalizability of these findings to broader populations. Given regional differences in epidemiology, co-infections, and healthcare infrastructure, further studies are urgently needed in other endemic regions, particularly in sub-Saharan Africa, Latin America, and the Pacific Islands. Further research, particularly large-scale, multicenter studies, is essential to validate these findings and enhance their applicability to diverse patient populations worldwide.

CONCLUSION

Moxidectin demonstrated comparable efficacy to placebo and ivermectin, with cure rates meeting non-inferiority thresholds relative to ivermectin and a high mean larvae reduction rate similar to ivermectin. Both moxidectin and ivermectin showed similarly mild and transient adverse events, underscoring moxidectin's safety profile. Moxidectin's advantages, including simplified dosing and a longer half-life, make it a promising alternative, particularly for populations at higher risk for re-infection or with limited healthcare services. However, given the limited number of studies and geographic concentration of existing research, further multicenter trials are necessary to confirm these findings across diverse patient populations and in broader geographic regions, including Africa, Latin America, and the Pacific Islands, and among immunocompromised populations to assess safety and efficacy in high-risk groups

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