Curr Treat Options Infect Dis (2019) 11:252–266
DOI 10.1007/s40506-019-00195-4

Neglected Tropical Diseases (A Sanchez, Section Editor)

Ivermectin for the Treatment of Soil-Transmitted Helmithiases

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Published online: 3 July 2019

This article is part of the Topical Collection on *Neglected Tropical Diseases*

Keywords Ivermectin · Soil-transmitted helminth · Geohelminth · Strongyloides · Trichuris

Abstract

Purpose of review To present ivermectin as a transformational tool for the control of neglected tropical diseases (NTDs) such as onchocerciasis and the drug of choice for the treatment of strongyloidiasis. Ivermectin is being re-discovered as a candidate drug for a variety of new indications among NTDs. In this review, new data are analyzed and put in context of current research interest as well as of the un-addressed issues for the treatment of soil-transmitted helminths (STH) infections.

Recent findings The addition of ivermectin to the benzimidazole drugs appears as the most promising solution for three key issues for the WHO-guided strategy for STH control; these issues are the low efficacy of the current regimens against *Trichuris trichiura*, the risk of emergence of benzimidazole resistance, and the inclusion of *Strongyloides stercoralis* in the strategy. Pharmacokinetic aspects of ivermectin along with the large experience in the treatment of intestinal helminths in veterinary medicine also show potential research paths for better utilization of this drug for human infections.

Summary New opportunities for the use of ivermectin in the control of STH as a public health problem are encouraging. However, this comes associated with new challenges not only of generating an adequate drug supply, but also for creating an access plan within a landscape of unresolved needs for the current indications.

Introduction

The history around the discovery, development, and utilization of ivermectin (IVM) in human public health are among the most successful case models in the struggle to control neglected tropical diseases (NTDs) [1]. Since the initial discovery by Satoshi Omura in the 1970s at Tokyo's Kitasato Institute until the present, IVM has been pivotal in the success of Mass Drug Administration (MDA) programs for onchocerciasis and lymphatic filariasis (LF) [2]. With over 800 million tablets shipped to the countries through the Mectizan Donation Program (MDP), the size of the donation has increased since 2014 [3••]. Despite this enormous amount of medication, the population that would benefit from IVM exceeds the number of persons reached by the onchocerciasis and LF programs.

Neglected tropical diseases are a group of infectious diseases that affect pediatric and adult populations in the world's poorest communities. Among the NTDs that cause significant global morbidity and mortality, soil-transmitted helminths (STH) infections (ascariasis, trichuriasis, and hookworm disease) are associated with malnutrition, impaired growth, and cognitive development in children [4]. Infections by *Strongyloides stercoralis*, also a STH of relevance, have been traditionally ignored in most surveys as well as by the World Health Organization's (WHO) control strategy. Although endemic throughout the tropics and sub-tropics, precise data on global prevalence are lacking, mostly due to technical difficulties in diagnosis [5].

The most recent estimates suggest that in 2015 428 million people were infected with hookworm (*Ancylostoma duodenale* and *Necator americanus*), 761 million with *Ascaris lumbricoides*, and 463 million with *Trichuris trichiura* [6]. These parasitic infections rank highest among NTDs in terms of disease burden: more than 3 million years lived with disability (YLDs) were attributable to STH infection, due to, wasting, stunting, gastrointestinal problems, and anemia [6].

Ivermectin is an endectocide drug, that is, an antiparasitic drug active both against endoparasites and ectoparasites. Current indications of IVM include treatment of infections by *Strongyloides stercoralis*, *Gnathostoma* spp., *Mansonella streptocerca*, and ectoparasites such as *Pediculus humanus* and *Sarcoptes scabiei*. In the field of STH, limitations in the efficacy of the currently available drugs call for a search of therapeutic options that could help in reaching global goals of disease control and elimination. New drugs or new formulations would prove useful in improvements in efficacy, prevention of drug resistance, and integration of regimens effective against *S. stercoralis* [7••, 8]. In that role, IVM appears as a suitable candidate, when used in coadministration with benzimidazole drugs currently prescribed for STH infections.

The aim of this review is to update on recent developments with regard to IVM. Based on the existing body of knowledge in veterinary medicine, IVM's pharmacodynamic and pharmacokinetic characteristics, as well as its safety profile, this review aims to identify the best approaches to generate evidence supporting the use and access of IVM against STH of human importance.

STH control strategy

STH are parasitic infections of particular importance in impoverished areas, exerting significant morbidity, mainly in the younger population through malnutrition and impairment of growth and development. In adults, they can also cause significant anemia (mostly hookworms) thus impairing productivity and well-being [9–11]. Despite differences in their clinical syndromes and mechanisms of infection, STH are transmitted in areas with inadequate water and sanitation [12]. Therefore, the most effective and sustainable control measures include structural improvements that lift communities from poverty and break the circle of poverty and disease [13]. The World Health Organization's STH control strategy emphasizes morbidity control through mass-drug administration (MDA), targeting preschool- and school-aged children and women of

childbearing age [14]. The global target is to eliminate morbidity due to STH in children by 2020, by treating at least 75% of population at risk, especially children in endemic areas (an estimated 873 million) [15]. At present, a strategic plan for beyond 2020 is being developed under WHO's leadership, which will probably include the control of strongyloidiasis, for which there are no large-scale public health deworming programs.

The benzimidazoles drugs, albendazole (ALB), and mebendazole (MBZ) are the most commonly used drugs to treat STH infections and are widely accessible for school-aged children through drug donation programs. Benzimidazoles have an excellent safety profile and are given to children as a single dose once or twice a year (depending on the estimated STH prevalence in the community) profile [16, 17]. While MDA programs remain the cornerstone for reducing STH morbidity, there are increasing concerns that the ongoing success of these programs may be hindered by important factors that relate to the monotherapy drug regimens used:

1. Low drug efficacy against *T. trichiura*: results from a recent systematic review and network meta-analysis suggest that although single-dose ALB remains efficacious against *A. lumbricoides* and hookworm (cure rate (CR) of 95.7% and 79.5% and egg reduction rate (ERR) of 98.5% and 89.6% respectively), efficacy against *T. trichiura* infections is considerably lower, (30.7% CR, and 49.9% ERR) [7••]. Of particular concern is the decreasing efficacy against *T. trichiura*; cure rates are estimated to have fallen from 38.6% in 1995 to as low as 16.4% in 2015.
2. Emergence of anthelmintic resistance: the use of widespread monotherapy could lead to parasite selection pressure that could empower resistance-type alleles surviving treatment [18]. In veterinary practice, benzimidazole resistance has been associated with single nucleotide polymorphisms (SNPs) in the β-tubulin isotype 1 gene [19].
3. *S. stercoralis*: while relying in the use of a single dose ALB or MBZ, the current strategy misses altogether any therapeutic activity against this nematode. Inclusion of *S. stercoralis* in the MDA strategy will require a change to the regimen. The current drug of choice for strongyloidiasis is IVM [20].

Based on the concerns outlined above, new anthelmintic drugs or drug combinations are considered a priority to increase the effectiveness of current interventions, widen the spectrum to include *S. stercoralis*, and lower the risk of anthelmintic resistance [21].

Pharmacology

As a chemical group, avermectins include a closely related 16-members macrocyclic lactone compounds (e.g1,. IVM, doramectin, abamectin, etc.) naturally produced by soil actinomycetes from the genus *Streptomyces* [22]. Fermentation of *Streptomyces avermitilis* produces four-related compounds named avermectin A1, A2, B1, and B2, which are further divided into different major and minor components. The major components are called A1a, A2a, B1a, B2a, and the less abundant as A1b, A2b, B1b and B2b. This particular nomenclature indicates a methoxyl (A) or hydroxyl (B) group at C_5, a double (1) or single (2) bond between C_{22} and C_{23}, and a secondary butyl group at C_{25} (a) or a single bond

with and hydroxyl group at C_{23} (b) [23]. Avermectin components are often commercialized as a mixture of "a" and "b" components. For example, IVM (22, 23-dihydroavermectin B1), the first commercially available macrocyclic lactone compound, is a mixture of not less than 80% of component "a" (B1a), and not more than 20% of component "b" (B1b), produced by the selective hydrogenation of avermectin B1. The notable success of IVM in veterinary medicine was based on a set of remarkable pharmacological properties: high efficacy, broad spectrum (endo and ectoparasites), high potency, low toxicity, long persistence, unique mode of action, and the possibility of being used by different routes of administration. Together, these properties made IVM the most widely used drug in the history of veterinary medicine worldwide [24].

Pharmacokinetic characteristics

The clinical efficacy of antiparasitic drugs is closely related to their affinity for a specific receptor (site of action), and also on the kinetic properties that facilitate achievement of effective drug concentrations at the site of action. The physicochemical properties of IVM determine their systemic concentration and the time of parasite exposure explaining, at least in part, the excellent efficacy and persistent activity of this compound [25]. IVM is a high molecular weight and highly lipophilic compound, exhibiting very low water solubility. Once absorbed, IVM is distributed throughout the body and reaches the different tissues to exert its antiparasitic effect (Table 1). Drug reaching lung and gastrointestinal mucosa/fluids explain the activity against lung and gastrointestinal nematodes, including adults as well as developing and hypobiotic stages [26]. A strong correlation between plasma and tissue (including gastrointestinal mucosa, lung, and skin) concentration profiles has been observed after its subcutaneous administration to cattle [27]. Concentrations attained in the tissues depend on the ability of the drug to penetrate capillary endothelium and diffuse across cell membranes, where lipophilicity plays a key role. An IVM plasma concentration between 0.5 and 1 ng/mL has been reported in cattle as the

Table 1. Main plasma pharmacokinetic parameters obtained for ivermectin (IVM) administered to different animal species including human

Animal species	Dose (mg/kg)	Administration route	Pharmacokinetic parameters			
			AUC (ng.d/mL)	Cmax (ng/mL)	Tmax (d)	T½el (d)
Cattle [25]	0.20	Subcutaneous	459 ± 47.4	42.8 ± 3.83	4.00 ± 0.94	17.2 ± 4.26
Sheep [31]	0.20	Oral	20.8 ± 12.3	8.67 ± 2.18	0.83 ± 0.26	1.57 ± 0.13
Goats [32]	0.20	Subcutaneous	61.8 ± 23.7	18.6 ± 6.02	0.87 ± 0.30	1.71 ± 0.64
Horses [33]	0.20	Oral	108 ± 10.9	30.1 ± 6.78	0.33 ± 0.33	5.48 ± 2.10
Pigs [28]	0.30	Subcutaneous	127 ± 6.89	39.6 ± 3.84	0.94 ± 0.16	3.80 ± 0.19
Dogs [34]	0.20	Subcutaneous	237 ± 41.5	116 ± 10.8	0.23 ± 0.09	3.32 ± 1.56
Humans [35]	0.20	Oral	39.0 ± 15.9	44.6 ± 18.0	0.17 ± 0.04	4.01 ± 1.40

AUC, area under the plasma concentration vs. time curve; *Cmax*, peak plasma concentration; *Tmax*, time to the Cmax; T½el, elimination half-life

minimal drug level required for optimal anthelmintic activity for most gastrointestinal/lung nematodes [28]. The disposition of IVM is characterized by their long persistence in the body and large volume of distribution, the significant effects of formulation and/or route of administration on their bioavailability, and the large interspecies and interindividual variations [29]. In most species IVM undergoes little metabolism and most of the dose is excreted unchanged in the feces (90%) with < 2% excreted in urine. Bile is the main route of excretion, with P-glycoprotein (P-gp) present in biliary canaliculi contributing to the drug's high fecal excretion [30].

Among different factors, it has been demonstrated that dose increment, route of administration, and body composition, all affect IVM systemic distribution in animals. IVM absorption was described to be proportional to the dose administered in ruminants [31]. Dose increments resulted in significantly enhanced drug efficacy against a resistant isolate of the abomasal (abomasum is the true stomach of ruminants) nematode *Haemonchus contortus* [31]. Macrocyclic lactones are reversibly exchanged between the bloodstream and the gastrointestinal tract [27]. The enhanced drug concentrations associated to the increasing doses account for gastrointestinal nematodes being exposed to toxic drug concentrations for extended periods of time. In humans, the systemic exposure of IVM (expressed as area under the concentration vs time curve (AUC) and peak concentration (Cmax), also resulted in increases after dose increment [35•, 36]. However, the impact that drug concentration increment related to the dose may have on the IVM effectiveness against endo and ectoparasites need to be determined. In any case, if efficacy studies are not accompanied by pharmacokinetic data, the high interindividual variability observed in humans [35•], may mask the effect associated with increased parasite exposure.

Shortly after its introduction into the veterinary market, when nematode susceptibility to IVM was high, equivalent efficacies against gastrointestinal parasites were observed after subcutaneous and oral administration [37]. However, in the presence of resistant nematodes, an improved efficacy of different macrocyclic lactone compounds has been reported after the oral compared to the subcutaneous treatment [33, 38–41]. Significantly higher IVM concentration profiles in the abomasal content and in *H. contortus* were measured after the oral treatment compared to the subcutaneous injection [40]. The transcuticular diffusion is the main route of access for different lipophillic substances, including IVM in gastrointestinal nematodes [42, 43]. Two major determinants of the rate of transfer across the nematode cuticle are drug lipophilicity [44] and concentration gradient [45]. Thus, the increased parasite drug exposure could explain the oral dose-related enhanced efficacy. In humans, IVM is mainly administered by the oral route. However, off-label subcutaneous administration has been used in patients suffering *Strongyloides* hyperinfection [46, 47].

Pharmacodynamic characteristics

IVM induce reduction in motor activity and paralysis in both, arthropods and nematodes. In nematodes, the paralytic effect can be observed on the pharynx and also the somatic musculature. These effects are mediated by its allosteric binding that irreversibly opens the glutamate (Glu)-gated chloride ion channel

receptor [48], mainly expressed in nematodes' neurons and muscle cells [49]. IVM can also activate others ligand-gated chloride channels as the gamma-aminobutyric acid (GABA) and glycine (Gly) receptors. The activation of GABA and Gly receptors requires much higher IVM concentrations than that required to activate the Glu receptors [50]. For this reason, this receptor constitutes the main target for macrocyclic lactone compounds. After IVM binding to its pharmacophore in the ligand-gated chloride channels, the opening of the chloride ion-selective pore allows chloride influx which hyperpolarizes the parasite's cell. This effect inhibits new action potentials, favoring the parasite's paralysis. Additionally, using *Caenorhabditis elegans* [51] or *Oesophagostomum dentatum* [52] as nematode models, it has been described that IVM also produces a profound inhibition in the opening frequency of the sodium channel nicotinic receptor.

Toxicity

Given at the recommended therapeutic doses, macrocyclic lactones are highly safe compounds. IVM toxicity in animals occurs associated to high doses and/or low P-glycoprotein expression in the capillary endothelial cells of the blood-brain barrier. IVM is a substrate of P-glycoprotein [53], which transports IVM out of the endothelial cells, protecting the nervous system from the IVM effect and reducing its toxicity risk. Some Collie dogs can be particularly sensitive to the toxic effect of IVM, due to a limited P-gp expression at the blood-brain barrier capillary endothelial cells. Signs of IVM toxicity in different animal species include neurotoxic signs such as depression, ataxia, mydriasis, salivation, tremors, convulsions, coma and, eventually, death. All these effects are likely associated to IVM binding to ligand-gated chloride channels at the central nervous system [54]. In humans, doses up to 10 times the usual doses in veterinary practice have been safely administered in healthy volunteers [55]. In patients, toxic effects have been most commonly observed in individuals infected with high burdens (> 20,000 microfilariae per milliliter of blood) of *Loa loa*, in which case, due to the potential severity of the adverse events, IVM is contraindicated [56, 57]. Pharmacovigilance through the VigiBase system revealed that serious neurological adverse events rarely occur beyond high burden *L. loa* infections [58]. Dose finding studies performed in a pediatric trial for the treatment of *T. trichiura* infections in Ivory Coast, demonstrated that regimens of 200, 400, and 600 μg had adverse event rates similar to placebo in terms of type, frequency, and severity [59••]. This raises hope in the search of regimens with improved efficacy using combination therapy coupled with higher doses of IVM and even multiple-day regimens [60]. Doses of 400 μg/kg have been tested in clinical trials to evaluate treatment for head lice in children. This dosage was well tolerated, although 1.8% of participants (7 of 398) discontinued treatment because of adverse events (similar to the control group receiving 0.5% malathion lotion) [61].

Uses in veterinary medicine

IVM was introduced in the early 80's into the veterinary pharmaceutical market as an injectable formulation (Ivomec®, Merck & Co.). In cattle, the animal

species in which IVM has been most extensively used, provided high level of efficacy (≥ 95%) and persistent (2–3 weeks) activity against gastrointestinal and lung nematodes (adult and immature stages, including hypobiotic larvae) [62]. Additionally, IVM is effective against economically important ectoparasites such as sucking lice, mites, and grubs [62]. IVM is not active against cestodes and trematodes. While in pigs IVM efficacy (0.30 mg/kg) against *Trichuris suis* was only 80% [62], in dogs a high efficacy (> 99%, 0.20 mg/kg) was reported against *Trichuris vulpis* [63], and at a lower dose (0.006 mg/kg) given at 1 month interval, is recommended for heartworm (*Dirofilaria immitis*) prevention. It has been also used against different endo and ectoparasites of laboratory, non-traditional, and exotic mammals, birds, fish, and reptiles.

Resistance

In animal production, the increasing selection pressure on the gastrointestinal nematodes after several years of intensive use of IVM favors the development of anthelmintic resistance. Resistance to IVM and to other related macrocyclic lactones is widespread, mainly in nematodes of sheep and goats but also in cattle [64]. Results of a study conducted on 62 beef farms in Argentina showed that resistance to IVM was present in 95% of the farms [65]. Despite the relevance of the IVM resistance phenomenon in ruminant nematodes, its genetic basis is poorly understood [66]. ATP binding-cassette (ABC) transporters have been proposed as non-target mechanisms of IVM resistance. For example, induction of P-gp expression in response to IVM treatment helps to explain nematode resistance to the macrocyclic lactones [67, 68]. Upregulation of transporter proteins increases drug elimination, protecting the parasite from its pharmacological effect.

In this context, MDA programs used to reduce parasite prevalence in human communities could be associated with the development of drug resistance. It is important to note that a high frequency of anthelmintic treatments increase the selection pressure favoring the emergence of drug resistance. For example, it has been reported that owners of cattle herds with presence of anthelmintic resistance treat animals at least four times per year, which is 2.1 times more than the treatments applied to herds harboring non-resistant nematodes [69]. With human MDA campaigns occurring just once or twice a year and targeting mostly school-aged children, the pressure for the selection of resistant parasites is significantly lower.

A new era for IVM

Usually called “the wonder drug”, IVM has been shown to have: (i) an unusually broad antiparasitic spectrum; (ii) a wide therapeutic index; and (iii) a novel mode of action, lacking cross-resistance with any commonly used anthelmintics [19]. IVM is recognized as a safe antiparasitic medicine approved for the treatment and control of human strongyloidiasis and scabies [5, 70], and has been safely used for decades in MDA campaigns for onchocerciasis and lymphatic filariasis (LF) [3••]. As an endectocide drug, IVM is also capable of killing arthropods, including some mosquito species of importance in human medicine, which has prompted its use in clinical trials for malaria control [71, 72].

Table 2. Efficacy of different anthelmintic drugs and drug combinations in selected randomized clinical trials against STH

Trichuris trichiura														
Site	**Outcomes**	**PLA**	**ALB**	**ALB × 3d**	**MBZ**	**IVM100**	**IVM200**	**IVM400**	**IVM600**	**ALB/IVM**	**MEB/IVM**	**ALB/DEC**	**DEC**	**Ref.**
Zanzibar	CR			43			11							[81]
	ERR			92			59							
Haiti	CR	28	53				44			80				[82]
	ERR	20	42				43			68				
Sri Lanka	CR		44							79		30		[83]
	ERR		70							94		69		
Philippines	CR		32				35			65		19	3	[84]
	ERR		54				87			98		79	20	
China	CR		68				67							[85]
	ERR		87				86							
Zanzibar	CR		10		19					38	55			[86]
	ERR		40		67					91	97			
Pemba	CR				8					28				[87]
	ERR				59					95				
Côte d'Ivoire	CR	20				12	21							[59••]
	ERR	68				63	54							
	CR	2					2	2	12					[59••]
	ERR	32					34	48	66					

PLA, placebo; *ALB*, albendazole 400 mg; *ALB × 3d*, albendazole 400 mg for 3 days; *MBZ*, mebendazole 500 mg; *IVM100*, ivermectin 100 µg/kg; *IVM200*, ivermectin 200 µg/kg; *IVM400*, ivermectin 400 µg/kg; *IVM600*, ivermectin 600 µg/kg; *DEC*, diethylcarbamazine

Table 3. Efficacy of different anthelmintic drugs and drug combinations in selected randomized clinical trials against STH

Ascaris lumbricoides									
Site	**Outcomes**	**PLA**	**ALB**	**MBZ**	**IVM200**	**ALB/IVM**	**ALB/DEC**	**DEC**	**Ref.**
Haiti	CR	37	98		94	100			[82]
	ERR	33	100		100	100			
Philippines	CR		70		78	78	78	24	[84]
	ERR		93		94	100	97	34	
China	CR		99		100				[85]
	ERR		99		100				
Pemba	CR			96		98			[87]
	ERR			100		100			

PLA, placebo; *ALB*, albendazole 400 mg; *MBZ*, mebendazole 500 mg; *IVM100*, ivermectin 100 μg/kg; *IVM200*, ivermectin 200 μg/kg; *DEC*, diethylcarbamazine

This activity against ectoparasites has also been observed in its efficacy for the treatment of *Pediculus humanus* or head lice [61]. This renewed interest in taking advantage of IVM as a tool for disease control beyond the original indications and uses is also defining more ambitious public health goals of disease elimination. This is the case of LF, where a triple drug regimen of ALB/IVM-diethylcarbamazine (DEC) has demonstrated in clinical trials its superior efficacy, which prompted its recommendation in the most recent WHO Guidelines for the treatment of LF [73, 74]; and also for STH. Mathematical modeling exercises suggest that transmission interruption goals would be feasible with the incorporation of IVM to benzimidazole regimens [75].

In terms of innovations, IVM also offers opportunities through its pharmacokinetic and pharmacodynamic properties; with millions of doses distributed and all the successes already experienced, it should be noticed that this drug offers opportunities for improvements that could facilitate its use. Starting from its potency, which allows dosing at the μg per kg range and its safety profile,

Table 4. Efficacy of different anthelmintic drugs and drug combinations in selected randomized clinical trials against STH

Hookworms								
Site	**Outcomes**	**PLA**	**ALB**	**ALB × 3d**	**MBZ**	**IVM200**	**ALB/IVM**	**Ref.**
Zanzibar	CR			88		0		[81]
	ERR			99		0		
Haiti	CR	13	100			64	100	[82]
	ERR	49	100			92	100	
China	CR		70			33		[85]
	ERR		90			80		
Pemba	CR				24		50	[87]
	ERR				60		95	

PLA, placebo; *ALB*, albendazole 400 mg; *ALB × 3d*, albendazole 400 mg for 3 days; *MBZ*, mebendazole 500 mg; *IVM200*, ivermectin 200 μg/kg

Table 5. Efficacy of different anthelmintic drugs and drug combinations in selected randomized clinical trials against STH

Strongyloides stercoralis							
Site	**Outcomes**	**ALB × 3d**	**MBZ**	**IVM200**	**IVM200 × 2**	**ALB/IVM**	**Ref.**
US/refuge	CR			100	95		[88]
Zanzibar	CR	45		83			[81]
Pemba	CR		86			100	[87]

ALB × 3d, albendazole 400 mg for 3 days; *MBZ*, mebendazole 500 mg; *IVM100*, ivermectin 100 µg/kg; *IVM200*, ivermectin 200 µg/kg

these are features that could potentially allow its co-formulation with other drugs without significant increases in pill size. This could lead to, a change in the prescription strategy into a fixed dose independent of body weight, very much like what is being applied for ALB or MBZ, among other drugs (such change, however, would imply using larger amounts of IVM). On this line, our group has demonstrated the safety and wide therapeutic range of IVM in a study with 54 healthy adult volunteers who received sequentially 200 µg/kg, a fixed dose of 18 mg and a fixed dose of 36 mg (using 18 mg IVM tablets) with no differences in type or severity of adverse events with doses of up to 700 µg/kg [35•].

IVM is currently manufactured for human use in oral formulations (tablets) of 3 or 6 mg. The initiative to develop an alternative dosing regimen for IVM in a fixed dose is based on the following concepts:

- IVM has demonstrated a wide therapeutic index, with hundreds of millions of doses ready distributed (at regular dosing) without toxicity issues [76].
- Current dosing strategies against onchocerciasis are based on the lack of increased efficacy with higher doses, but not due to toxicity issues [77].
- High doses of IVM have been tested in other studies and have shown an excellent safety profile: in adults, doses up to 10 times the 200 µg/kg have been tested in a small group of participants and showed the same rate of adverse events as placebo [55].

The case for including IVM in STH control

A recent report of the WHO Expert Committee on Selection and Use of Essential Medicines acknowledged the favorable benefit-to-harm ratio of IVM and its potential public health impact in the treatment of STH, including *S. stercoralis* [78]. The report concluded that the evidence demonstrates IVM to be a highly efficacious treatment of *S. stercoralis* and that a regimen combining IVM with ALB or MBZ provides improved efficacy against *T. trichiura*. The evidence supporting the case of IVM in STH is accumulating through observational studies in areas where IVM has been used against onchocerciasis as in Ecuador, where Anselmi et al retrospectively identified significant reduction in the prevalence of strongyloidiasis after several years of MDA of IVM for onchocerciasis [79]. However, these observations have not been consistent throughout regions

where unaccounted factors such as drug coverage and water and sanitation interfere with accurate assessments of efficacy and effectiveness, making it impossible to demonstrate significant impact [80]. The stronger evidence is, however, originating from randomized clinical trials where in controlled environments, different regimens are compared and evaluated for safety and efficacy (Tables 2, 3, 4, and 5).

The superior efficacy of combined regimens of IVM with ALB or MBZ against *T. trichiura* has been the conclusion of a recent meta-analysis based on an analysis of four clinical trials that fulfill the criteria for inclusion in the analysis, revealing that compared with ALB alone, the use of ALB/IVM rendered a risk ratio of 0.44 (95% confidence interval 0.31–0.62); for *A. lumbricoides* and hookworms, the superiority of the combination regimen was not demonstrated [89•]. Another clinical trial performed in Ivory Coast looking at the efficacy of IVM monotherapy against *T. trichiura* found a poor efficacy of regimens of up to 600 μg/kg [59••].

The current use of IVM is restricted to individuals weighing ≥ 15 kg. This limitation, which is not based on evidence demonstrating either lack of efficacy or added toxicity, represents an obstacle in two different aspects of public health: (1) Excludes significant groups of the at-risk population from the benefits of IVM; (2) By lowering the absolute coverage of the interventions, it decreases the likelihood of transmission interruption and disease elimination; highlighting the need to collect evidence on PK, safety, and efficacy in the younger age population.

The sub-optimal efficacy of IVM against *T. trichiura* and hookworm could be related, at least in part, to a low exposure to IVM. There are two potential routes of drug entry into gastrointestinal nematodes, the oral ingestion or the transcuticular diffusion. Since hookworms feed on blood, systemic drug concentrations could be relevant in order to predict activity. However, it has been demonstrated that even for hematophagous sheep nematodes such as *Haemonchus contortus*, the main route of IVM and ALB entry is by transcuticular diffusion from the abomasal fluid [31] . Altogether, these findings confirm the relevance of the transcuticular absorption process as a main route of drug entry into gastrointestinal nematodes. Therefore, drug concentration achieved in the gastrointestinal fluids or in the mucous layer of gastrointestinal mucosa determines the amount of drug reaching the parasite and, consequently, drug efficacy. The anthelmintic activity could theoretically be improved by increasing the active drug concentrations at the site of parasite location. The uses of higher and/or repeated doses are two basic strategies to increase parasite exposure to IVM. In the area of veterinary medicine, an improved efficacy against an IVM-resistant *H. contortus* isolate was associated to dose increments [31].

Conclusion

It is becoming apparent that IVM is a significant tool for the control of STH, the same way it has proved crucial for other NTDs. Research gaps being filled for the understanding of antiparasitic efficacy and overall safety, need complementary efforts to better understand its safety in groups particularly vulnerable to these infections, such as young children and pregnant women. Coupled with the above, and in view of the growing list of indications for IVM, a deeper proper

understanding of the interactions between the drug's demand and supply is necessary in order to achieve the ultimate goal of improving health indicators in communities affected by STH and other diseases related to poverty.

Compliance with ethical standards

Conflict of interest
Alejandro J. Krolewiecki declares that he has no conflicts of interest. Luis Alvarez declares that he has no conflicts of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Omura S, Crump A. Ivermectin: panacea for resource-poor communities? Trends Parasitol. 2014;30:445–55.
2. Crump A, Ōmura S. Ivermectin, "wonder drug" from Japan: the human use perspective. Proc Jpn Acad Ser B Phys Biol Sci. 2011;87:13–28.
3.•• World Health Organization (WHO). Weekly epidemiological record: summary of global update on preventive chemotherpy implementation in 2016: crossing the billion. 2017;92:589–608.

WHO report on the size and reaches of the current preventive chemotherapy campaigns against NTDs.

4. Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. Lancet Elsevier Ltd. 2017;6736:1–14.
5. Krolewiecki A, Nutman TB. Strongyloidiasis: a neglected tropical disease. Infect Dis Clin N Am. 2019;33:135–51.
6. Vos T, Allen C, Arora M, Barber RM, Brown A, Carter A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the global burden of disease study 2015. Lancet. 2016;388:1545–602.
7.•• Moser W, Schindler C, Keiser J. Efficacy of recommended drugs against soil transmitted helminths: systematic review and network meta-analysis. BMJ BMJ Publishing Group. 2017;358:j4307.

Up-to-date analysis of anthelmintic efficacy against STH using a meta-analysis approach.

8. Becker SL, Liwanag HJ, Snyder JS, Akogun O, Belizario V, Freeman MC, et al. Toward the 2020 goal of soil-transmitted helminthiasis control and elimination. PLoS Negl Trop Dis. 2018;12:e0006606.
9. Stephenson L, Latham MC, Klnotl SN, Pertet A, Adams J. Physical fitness, growth and appetite of Kenyan school boys with hookworm , Trichuris trichiura and Ascaris lumbricoides infections are improved four months after a single dose of albendazole, vol. 1081; 1993. p. 1036–46.
10. Ezeamama AE, Friedman JF, Acosta LP, Bellinger DC, Langdon GC, Manalo DL, et al. Helminth infection and cognitive impairment among Filipino children. Am J Trop Med Hyg. 2005;72:540–8.
11. Echazu A, Juarez M, Vargas PA, Cajal SP, Cimino O, Heredia V, et al. Albendazole and ivermectin for the control of soil-transmitted helminths in an area with high prevalence of Strongyloides stercoralis and hookworm in northwestern Argentina: a community-based pragmatic study. PLoS Negl TropDis. 2017;11(10): e0006003.
12. Echazú A, Bonanno D, Juarez M, Cajal SP, Heredia V, Caropresi S, et al. Effect of poor access to water and sanitation as risk factors for soil-transmitted helminth infection: selectiveness by the infective route. PLoS Negl Trop Dis. 2015;9:1–14.
13. Boisson S, Engels D, Gordon BA, Medlicott KO, Neira MP, Montresor A, et al. Water, sanitation and hygiene for accelerating and sustaining progress on neglected tropical diseases: a new global strategy 2015–20. Int Heal. 2016;8:i19–21.
14. World Health Organization (WHO)Guideline: preventive chemotherapy to control soil-transmitted

helminth infections in at-risk population groups. Geneva; 2017.
15. De Rochars MB, Direny AN, Roberts JM, Addiss DG, Radday J, Beach MJ, et al. Community-wide reduction in prevalence and intensity of intestinal helminths as a collateral benefit of lymphatic filariasis elimination programs. Am J Trop Med Hyg. 2004;71:466–70.
16. Urbani C, Albonico M. Anthelminthic drug safety and drug administration in the control of soil-transmitted helminthiasis in community campaigns. Acta Trop. 2003;86:215–21.
17. Gabrielli A-F, Montresor A, Chitsulo L, Engels D, Savioli L. Preventive chemotherapy in human helminthiasis: theoretical and operational aspects. Trans R Soc Trop Med Hyg. 2011;105:683–93.
18. Vercruysse J, Albonico M, Behnke JM, Kotze AC, Prichard RK, McCarthy JS, et al. Is anthelmintic resistance a concern for the control of human soil-transmitted helminths? Int J Parasitol Drugs Drug Resist. 2011;1:14–27.
19. Geary TG, Woo K, McCarthy JS, Mackenzie CD, Horton J, Prichard RK, et al. Unresolved issues in anthelmintic pharmacology for helminthiases of humans. Int J Parasitol. 2010;40:1–13.
20. Krolewiecki AJ, Lammie P, Jacobson J, Gabrielli A-FF, Levecke B, Socias E, et al. A public health response against Strongyloides stercoralis: time to look at soil-transmitted helminthiasis in full. PLoS Negl Trop Dis. 2013;7:e2165.
21. Brooker SJ. Soil-transmitted helminth treatment: multiple-drug regimens. Lancet Infect Dis Elsevier Ltd. 2018;18:698–9.
22. Burg RW, Miller BM, Baker E, Birnbaum J, Currie SA. Avermectins, a new family of potent anthelmintics agents: producing organism and fermentation. Ant A Chem. 1979;15:361–7.
23. Shoop WL, Mrozik H, Fisher MH. Structure and activity of avermectins and milbemycins in animal health. Vet Parasitol. 1995;59:139–56.
24. Laing R, Gillan V, Devaney E. Ivermectin – old drug, new tricks? Trends Parasitol Elsevier Ltd. 2017;33:463–72.
25. Lanusse C, Lifschitz A, Virkel G, Alvarez L, SAnchez S, Sutra JF, et al. Comparative plasma disposition kinetics of ivermectin, moxidectin and doramectin in cattle. J Vet Pharmacol Ther [Internet. 1997;20:91–9.
26. Egerton JR, Eary CH, Suhayda D. The anthelmintic efficacy of ivermectin in experimentally infected cattle. Vet Parasitol. 1981;8:59–70.
27. Lifschitz A, Virkel G, Sallovitz J, Sutra JF, Galtier P, Alvinerie M, et al. Comparative distribution of ivermectin and doramectin to parasite location tissues in cattle. Vet Parasitol. 2000;87:327–38.
28. Lifschitz A, Pis A, Alvarez L, Virkel G, Sánchez S, Sallovitz J, et al. Bioequivalence of ivermectin formulations in pigs and cattle. J Vet Pharmacol Ther. 1999;22:27–34.
29. McKellar QA, Benchaoui HA. Avermectins and milbemycins. J Vet Pharmacol Ther. 1996;19:331–51.
30. Laffont CM, Toutain PL, Alvinerie M, Bousquet-Melou A. Intestinal secretion is a major route for parent ivermectin elimination in the rat. Drug Metab Dispos. 2002;30:626–30.
31. Alvarez L, Suarez G, Ceballos L, Moreno L, Canton C, Lifschitz A, et al. Integrated assessment of ivermectin pharmacokinetics, efficacy against resistant Haemonchus contortus and P-glycoprotein expression in lambs treated at three different dosage levels. Vet Parasitol Elsevier BV. 2015;210:53–63.
32. Lifschitz A, Nava S, Guglielmone AA, Imperiale F, Farias C, Mangold AJ, et al. Failure of ivermectin and eprinomectin to control Amblyomma parvum in goats: characterization of acaricidal activity and drug pharmacokinetic disposition. Vet Parasitol. 2008;156:284–92.
33. Saumell C, Lifschitz A, Baroni R, Fusé L, Bistoletti M, Sagües F, et al. The route of administration drastically affects ivermectin activity against small strongyles in horses. Vet Parasitol [Internet] Elsevier BV. 2017;236:62–7.
34. Gokbulut C, Karademir U, Boyacioglu M, McKellar QA. Comparative plasma dispositions of ivermectin and doramectin following subcutaneous and oral administration in dogs. Vet Parasitol. 2006;135:347–54.
35.• Muñoz J, Ballester MR, Antonijoan RM, Gich I, Rodríguez M, Colli E, et al. Safety and pharmacokinetic profile of fixed-dose ivermectin with an innovative 18mg tablet in healthy adult volunteers. PLoS Negl Trop Dis. 2018;12(1):e0006020.
This study explores fixed dose regimens with detailed pharmacokinetic parameters of ivermectin.
36. Gonzalez Canga A, Sahagun Prieto AM, Diez Liebana MJ, Fernandez Martinez N, Sierra Vega M, Garcia Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans–a mini-review. AAPS J. 2008;10(1):42–6.
37. Lespine A, Alvinerie M, Sutra JF, Pors I, Chartier C. Influence of the route of administration on efficacy and tissue distribution of ivermectin in goat. Vet Parasitol. 2005;128:251–60.
38. Gopal RM, West DM, Pomroy WE. The difference in efficacy of ivermectin oral, moxidectin oral and moxidectin injectable formulations against an ivermectin-resistant strain of Trichostrongylus colubriformis in sheep. N Z Vet J. 2001;49:133–7.
39. Alka GRM, Sandhu KS, Sidhu PK. Efficacy of abamectin against ivermectin-resistant strain of Trichostrongylus colubriformis in sheep. Vet Parasitol. 2004;121:277–83.
40. Lloberas M, Alvarez L, Entrocasso C, Virkel G, Lanusse C, Lifschitz A. Measurement of ivermectin concentrations in target worms and host gastrointestinal tissues: influence of the route of administration on the activity against resistant Haemonchus contortus in lambs. Exp Parasitol. 2012;131:304–9.
41. Canton C, Canton L, Domínguez MP, Moreno L, Lanusse C, Alvarez L, et al. Field trial assessment of ivermectin pharmacokinetics and efficacy against

susceptible and resistant nematode populations in cattle. Vet Parasitol. 2018;256:43–9.
42. Cross HF, Renz A, Trees AJ. In-vitro uptake of ivermectin by adult male Onchocerca ochengi. Ann Trop Med Parasitol. 1998;92:711–20.
43. Alvarez LI, Mottier ML, Lanusse CE. Drug transfer into target helminth parasites. Trends Parasitol. 2007;23:97–104.
44. Mottier ML, Alvarez LI, Pis MA, Lanusse CE. Transtegumental diffusion of benzimidazole anthelmintics into Moniezia benedeni: correlation with their octanol-water partition coefficients. Exp Parasitol. 2003;103:1–7.
45. Mottier L, Alvarez L, Ceballos L, Lanusse C. Drug transport mechanisms in helminth parasites: passive diffusion of benzimidazole anthelmintics. Exp Parasitol. 2006;113:49–57.
46. Pacanowski J, Dos Santos M, Roux A, Le Maignan C, Guillot J, Lavarde V, et al. Subcutaneous ivermectin as a safe salvage therapy in Strongyloides stercoralis hyperinfection syndrome: a case report. Am J Trop Med Hyg. 2005;73:122–4.
47. Barrett J, Broderick C, Soulsby H, Wade P, Newsholme W. Subcutaneous ivermectin use in the treatment of severe Strongyloides stercoralis infection: two case reports and a discussion of the literature. J Antimicrob Chemother. 2016;71:220–5.
48. Hibbs R, Gouaux E. Principles of activation and permeation in an anion-selective cys-loop receptor. Nature. 2011;474:54–60.
49. Cully DF, Vassilatis DK, Liu KK, Paress PS, Van der Ploeg LH, Schaeffer JM, et al. Cloning of an avermectin-sensitive glutamate-gated chloride channel from Caenorhabditis elegans. Nature. 1994;371:707–11.
50. Adelsberger H, Lepier A, Dudel J. Activation of rat recombinant alpha(1)beta(2)gamma(2S) GABA(A) receptor by the insecticide ivermectin. Eur J Pharmacol. 2000;394:163–70.
51. Hernando G, Bouzat C. Caenorhabditis elegans neuromuscular junction: GABA receptors and ivermectin action. PLoS One. 2014;9:e95072.
52. Abongwa M, Buxton SK, Robertson AP, Martin RJ. Curiouser and curiouser: the macrocyclic lactone, abamectin, is also a potent inhibitor of pyrantel/tribendimidine nicotinic acetylcholine receptors of gastro-intestinal worms. PLoS One. 2016;11:1–14.
53. Didier AD, Loor F. The abamectin derivative ivermectin is a potent Pglycoprotein inhibitor. Anti-Cancer Drugs. 1996;7:745–51.
54. Lankas G, Gordon R. Toxicology. In: Campbell W, editor. Ivermectin and abamectin. New York: Springer–Verlag; 1989.
55. Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol. 2002;42:1122–33.
56. Gardon J, Gardon-Wendel N, Demanga-Ngangue KJ, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. Lancet. 1997;350:18–22.
57. Boussinesq M, Gardon J, Gardon-Wendel N, Chippaux J-P. Clinical picture, epidemiology and outcome of Loa-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon. Filaria J. 2003;2 Suppl 1:S4:S4.
58. Chandler RE. Serious neurological adverse events after ivermectin-do they occur beyond the indication of onchocerciasis? Am J Trop Med Hyg. 2018;98:382–8.
59.•• Wimmersberger D, Coulibaly JT, Schulz J, Puchkow M, Huwyler J, N'Gbesso Y, et al. Efficacy and safety of ivermectin against Trichuris trichiura in preschool- and school-aged children: a randomized controlled dose-finding trial. Clin Infect Dis. 2018;67:1247–55.
Randomized clinical trial on the role of IVM against T. trichiura infections.
60. Krolewiecki AJ. Misconceptions and paradoxes in soil-transmitted helminthiases control as a public health problem. PLoS Negl Trop Dis. 2018;12(9):e0006672.
61. Izri A, Hofmann R, Ph D, Mann SG, Burgess I, Ph D, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. N Engl J Med. 2010;362:896–905.
62. Benz GW, Roncalli RA, Gross SJ. Use of ivermectin in cattle, sheep, goats, and swine. In: Campbell W, editor. Ivermectin and abamectin. New York: Springer–Verlag; 1989.
63. Anderson DL, Roberson EL. Activity of ivermectin against canine intestinal helminths. Am J Vet Res. 1982;43:1681–3.
64. Kaplan RM. Drug resistance in nematodes of veterinary importance: a status report. Trends Parasitol. 2004;20:477–81.
65. Cristel S, Fiel C, Anziani O, Descarga C, Cetrá B, Romero J, et al. Anthelmintic resistance in grazing beef cattle in central and northeastern areas of Argentina — an update. Vet Parasitol Reg Stud Reports. 2017;9:25–8.
66. Kotze AC, Hunt PW, Skuce P, von Samson-Himmelstjerna G, Martin RJ, Sager H, et al. Recent advances in candidate-gene and whole-genome approaches to the discovery of anthelmintic resistance markers and the description of drug/receptor interactions. Int J Parasitol Drugs Drug Resist Australian Society for Parasitology. 2014;4:164–84.
67. Xu M, Molento M, Blackhall W, Ribeiro P, Beech R, Prichard R. Ivermectin resistance in nematodes may be caused by alteration of P-glycoprotein homolog. Mol Biochem Parasitol. 1998;91:327–35.
68. Prichard RK, Roulet A. ABC transporters and beta-tubulin in macrocyclic lactone resistance: prospects for marker development. Parasitology. 2007;134:1123–32.
69. Suarez VH, Cristel SL. Anthelmintic resistance in cattle nematode in the western Pampeana Region of Argentina. Vet Parasitol. 2007;144:111–7.

70. Romani L, Whitfeld MJ, Koroivueta J, Kama M, Wand H, Tikoduadua L, et al. Mass drug administration for scabies control in a population with endemic disease. N Engl J Med. 2015;373:2305–13.
71. Kobylinski KC, Foy BD, Richardson JH. Ivermectin inhibits the sporogony of plasmodium falciparum in Anopheles gambiae. Malar J. 2012;11:381.
72. Smit MR, Ochomo EO, Aljayyoussi G, Kwambai TK, Abong'o BO, Chen T, et al. Safety and mosquitocidal efficacy of high-dose ivermectin when co-administered with dihydroartemisinin-piperaquine in Kenyan adults with uncomplicated malaria (IVERMAL): a randomised, double-blind, placebo-controlled trial. Lancet Infect Dis. Elsevier Ltd. 2018;18:615–26.
73. Fischer PU, King CL, Jacobson JA, Weil GJ. Potential value of triple drug therapy with ivermectin, diethylcarbamazine, and albendazole (IDA) to accelerate elimination of lymphatic filariasis and onchocerciasis in Africa. PLoS Negl Trop Dis. 2017;11:1–10.
74. World Health Organization. Guideline: alternative mass drug administration regimens to eliminate lymphatic filariasis. Guidel Altern Mass Drug Adm Regimens to Elimin Lymphat Filariasis. 2017. https://www.who.int/lymphatic_filariasis/resources/9789241550161/en/. Accessed 11 Apr 2019.
75. Turner HC, Truscott JE, Bettis AA, Hollingsworth TD, Brooker SJ, Anderson RM. Analysis of the population-level impact of co-administering ivermectin with albendazole or mebendazole for the control and elimination of Trichuris trichiura. Parasite Epidemiol Control. 2016;1:177–87.
76. Hopkins AD, Molyneux DH. A decade of ivermectin-albendazole donation for lymphatic filariasis. Ann Trop Med Parasitol. 2009;103 Suppl 1:S3:3.
77. Awadzi K, Attah SK, Addy ET, Opoku NO. The effects of high-dose onchocerciasis patients ivermectin regimens on Onchocerca volvu/us in. 1999;
78. WHO. The selection and use of essential medicines: report of the WHO expert committee (including the 20th WHO model list of essential medicines and the 6th WHO model list of essential medicines for children). Geneva; 2017. (WHO technical report series; no. 1006). Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf;jsessionid=5505ACD64A72393DBAF1F8C3E18138B6?sequence=1. Accessed 11 Apr 2019.
79. Anselmi M, Buonfrate D, Guevara Espinoza A, Prandi R, Marquez M, Gobbo M, Montresor A, Albonico M, Racines Orbe M, Martin Moreira J, Bisoffi Z Mass administration of ivermectin for the elimination of onchocerciasis significantly reduced and maintained low the prevalence of strongyloides stercoralis in Esmeraldas, Ecuador. PLoS Negl Trop Dis. 2015;9(11):e0004150.
80. Oluwole AS, Isiyaku S, Aliero AA, Nwosu C, William A, Elhassan E, et al. Assessment of the burden of soil-transmitted helminthiasis after five years of mass drug administration for onchocerciasis and lymphatic filariasis in Kebbi State, Nigeria. Parasite Epidemiol Control The Authors. 2017;2:21–9.
81. Marti H, Haji J, Savioli L, Chwaya HM, Mgeni A, Ameir S, et al. A comparative trial of a single-dose ivermectin versus three days of albendazole for the treatment of Strongyloide stercoralis infections and other soil-transmitted helminth infections in children. AmJTropMedHyg. 1996;55:477–81.
82. Beach MJ, Streit TG, Addiss DG, Prospere R, Roberts JM, Lammie PJ. Assessment of combined ivermectin and albendazole for treatment of intestinal helminth and Wuchereria bancrofti infections in Haitian schoolchildren. Am J Trop Med Hyg. 1999;60:479–86.
83. Ismail MM, Jayakody RL. Efficacy of albendazole and its combinations with ivermectin or diethylcarbamazine (DEC) in the treatment of Trichuris trichiura infections in Sri Lanka. Ann Trop Med Parasitol. 1999;93:501–4.
84. Belizario VY, Amarillo ME, De LWU, Reyes AEDL, Bugayong MG, Macatangay BJC. A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against Ascaris and Trichuris spp, vol. 81; 2003. p. 35–42.
85. Wen L, Yan X, Sun F, Fang Y, Yang M, Lou L, et al. A randomized , double-blind , multicenter clinical trial on the efficacy of ivermectin against intestinal nematode infections in China, vol. 106; 2008. p. 190–4.
86. Knopp S, Mohammed KA, Speich B, Khamis IS. Efficacy of albendazole and mebendazole alone or in combination with ivermectin against Trichuris trichiura and other soil-transmitted helminths control of helminthiases in Zanzibar; 2009. p. 1–12.
87. Speich B, Ali SM, Ame SM, Bogoch II, Alles R, Huwyler J, et al. Efficacy and safety of albendazole plus ivermectin, albendazole plus mebendazole, albendazole plus oxantel pamoate, and mebendazole alone against Trichuris trichiura and concomitant soil-transmitted helminth infections: a four-arm, randomised controlled t. Lancet Infect Dis. 2015;15:277–84.
88. Gann P, Neva F, Gam A. A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. J Infect Dis. 1994;169:1076–9.
89.•• Palmeirim MS, Hürlimann E, Knopp S, Speich B, Belizario V, Joseph SA, et al. Efficacy and safety of co-administered ivermectin plus albendazole for treating soil-transmitted helminths: a systematic review meta-analysis and individual patient data analysis. PLoS Negl Trop Dis. 2018;12:1–26.
A systematic review providing up-to-date information of trials using albendazole and ivermectin in combination.

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