Expert Opinion

Pharmacotherapy of helminth infection

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Background: In the first decade of the 21st century, worm infections are still very common, especially – but not exclusively – in the developing world. *Objective*: To review the current pharmacotherapy of the major trematode, cestode and nematode infections of humans. *Methods*: A systematic search of the Cochrane Databank of Controlled Trials and PubMed with MeSH terms (anthelmint* or treatment or therapy) and (cestoda or trematoda or nematoda or specific helminth species or specific medication). Further references were obtained from article biobliographies. *Results*: Three hundred and twenty-six publications were selected for further review. *Conclusion*: Albendazole, praziquantel and ivermectin are the most important anthelmintics available, easy to use and active against most helminths. Diethylcarbamazine is used in loasis and lymphatic filariasis. Doxycycline can eliminate endosymbiotic bacteria of certain filariae, but its place in therapy needs to be further defined. In the treatment of cystic hydatid disease, a better, non-caustic protoscolicidal drug would diminish the complication rate of current puncture–aspiration–injection–reaspiration treatment. The reliance on so few drugs creates a dangerous situation for development of resistance. Triclabendazole is a welcome addition for fascioliasis. Tribendimidine, artemisinine derivatives and nitazoxanide are promising products, but their therapeutic place needs to be further defined.

Keywords: anthelmintics, cestoda, nematoda, therapy, trematoda

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1. Introduction

Worm infections result in an important burden on humanity, leading to the loss of millions of disability-adjusted life years. In several countries, socio-economic development, sanitation and health education combined with anthelmintic treatment are key factors in preventing new cases and curing existing worm infections. Access to treatment is a key factor as infections occur disproportionately among the poor living in the developing world. The reasons for treatment vary. Treatment can be undertaken to reach total elimination of worms in an individual or can be targetted at interrupting transmission in a population, with the purpose of large-scale prevention of morbidity or eliminating the infection as a public health problem. Many worms are longlived and quick spontaneous cure cannot be expected for several of them. Resistance to reinfection is generally low. Only a few drugs are used for the treatment and control of these diseases. For some, there is no good anthelmintic available yet. It is feared that reliance on the current limited number of anthelmintics will become problematic in the future due to the development of anthelmintic resistance.

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2. Anthelmintics

2.1 Levamisole

Levamisole (*l*-tetramisole) is a synthetic phenylimidazolthiazole that was introduced in 1966 as an anthelmintic agent against soil-transmitted nematodes. It has immunomodulating activity [1]. It has been used to restore depressed immune function and as adjuvant in the treatment of colon carcinoma. Combined treatment with mebendazole and levamisole may be useful as a tool to delay the development of benzimidazole resistance [2]. At present, it has limited indications as an anthelmintic in human therapy, if alternatives are available.

2.2 Pyrantel pamoate and analogues

Pyrantel is a pyrimidine derivative that acts as a cholingeric depolarizing neuromuscular agent, inducing persistent activation of nicotinic acetylcholine receptors, which results in spastic paralysis of the worms, allowing them to be expelled. Oxantel is an m-oxyphenol analogue of pyrantel. Pyrantel can be formulated as the pamoate or embonate salt. Pyrantel pamoate is rather insoluble and is, therefore, restricted in distribution in the gut. Most of the drug is eliminated in the feces whereas a minor fraction (15%) is excreted in the urine [3]. It is inactive against tissue dwelling parasites. Single-dose oral pyrantel for ascariasis resulted in cure rates of 88% [4]. For ascariasis, pyrantel-oxantel (10 mg/kg) reached cure rates of 96% [5]. Cure rates of enterobiasis are influenced by treatment of nearby carriers, for example, in family or class mates [6]. In the case of pinworm, it is advised to repeat the treatment after 2 weeks. Several doses are needed for hookworm infection, as the efficacy of single-dose oral pyrantel pamoate against hookworm infections is only 31% [4]. Pyrantel-resistant *Ancylostoma duodenale* has been described [7]. Pyrantel is effective in oesophagostomiasis [8]. For trichuriasis a single dose pyrantel achieves a cure rate of 28% [4]. Transient and mild gastrointestinal symptoms occasionally are observed in humans, as are headache, dizziness, rash and fever.

2.3 Metrifonate

Metrifonate is an organophosphorus compound used first as an insecticide and later as an anthelmintic for treatment of *Schistosoma haematobium*. Metrifonate is a prodrug, which is converted nonenzymatically to dichlorvos, a potent long-acting cholinesterase inhibitor. Inhibition of cholinesterase alone is unlikely to explain the antischistosomal properties of metrifonate [9]. Metrifonate is effective clinically only against infections with *S. haematobium*. *Schistosoma mansoni* can detoxify dichlorvos through a glutathione-dependent pathway [10]. This helps to explain why this species is normally refractory to this medication, although *in vitro* dichlorvos is about as equally potent as an inhibitor of both *S. mansoni* and *S. haematobium* acetylcholinesterases. Metrifonate requires several administrations and is, therefore, operationally less convenient in community-based control programs. At present, metrifonate has been withdrawn from the market, but it is possible that it will be reconsidered for the WHO Model List of Essential Medicines [11].

2.4 Bithionol

Bithionol is a halogenated phenol derivative with a sulfur bridge. It used to be the first-line agent for fascioliasis [12]. At present, it has been replaced by triclabendazole for this indication. It was also used against paragonomiasis. Adverse cutaneous and gastrointestinal effects included photosenstitivity, vomiting, diarrhea, urticaria and abdominal pain.

2.5 Piperazine

Piperazine is a cyclic secondary amine. A large number of substituted piperazine derivatives exhibit anthelmintic activity [13]. Piperazine is effective against ascariasis and enterobiasis. It can be used for treatment of these infections as an alternative to mebendazole or pyrantel pamoate. The drug acts as a GABA receptor agonist and induces flaccid paralysis in the worm, which results in its expulsion [14]. The recommended dose for ascariasis is 75 mg/kg for 2 days (max 3.5 g for adults; max 2.5 g for children 2 – 12 years). For enterobiasis 50 mg/(kg day) for 7 days is recommended. Two or more courses should be given at 1 – 2 weeks interval [3]. Adverse effects include gastrointestinal upset, transient neurological effects and urticaria. At lethal doses convulsions and respiratory depression occur. It is contraindicated in epileptic patients.

2.6 Oxamniquine

Oxamniquine is a tetrahydroquinoline derivative distantly related to hycanthone. It was used to treat infections with *S. mansoni*, especially in South America [15]. Most strains of *S. mansoni* are highly susceptible to oxamniquine (especially male worms), but resistance of *S. mansoni* to oxamniquine in Brazil has been well documented [16]. *S. haematobium* and *S. japonicum* are virtually unaffected by therapeutic doses. Oxamniquine is well tolerated, with occasional side effects of headache, dizziness, drowsiness and gastrointestinal disturbances. Oxamniquine has become difficult to obtain.

2.7 Niclosamide

Niclosamide is a halogenated salicylanilide derivative and was introduced in the 1960s for human use as a taeniacide. It inhibits energy production in the parasite. It is not active against nematodes. The ethanolamine salt of niclosamide can be used as a molluscicide, for example, in snail control of schistosomiasis. Niclosamide is on the WHO 15th Model List of Essential Medicines for use when praziquantel treatment fails. It is used for treatment of human intestinal infections with *Taenia saginata, Diphyllobothrium latum, Hymenolepis nana* and most other adult cestodes [17]. For taeniasis, a single dose (2000 mg for an adult) is sufficient. For hymenolepiasis an extended course is needed [18]. Niclosamide is no longer approved

for use in the US. A cream formulation might protect against cercarial dermatitis [19].

2.8 Niridazole

Niridazole is a nitrothiazole derivative. It is an antischistosomal agent that has become obsolete because praziquantel became available [20]. It was also used against dracunculiasis. It had important side effects, including ECG changes, agitation, confusions, hallucinations, convulsions and induction of transient defective spermatogenesis [3,21].

2.9 Benzimidazoles

2.9.1 Benzimidazoles, general

The benzimidazole class of anthelmintics includes four main drugs for human use: thiabendazole, mebendazole, albendazole and triclabendazole. Flubendazole is rarely used in human treatment. Benzimidazoles exert their main anthelmintic effect by binding to free β-tubulin, thereby inhibiting polymerization of tubulin [22]. The selective toxicity of these agents results because benzimidazoles bind parasite β-tubulin with much higher affinity than the mammalian protein. Benzimidazole resistance in certain nematodes involves selection of mutant β-tubulin gene isotypes [23]. Benzimidazoles are widespread in their use in global control programs for both soil-transmitted helminthiases and filarial infections. Post-treatment catch-up growth, improved iron status, and improvements in childhood intellectual and cognitive development were seen in children after single-dose treatment with albendazole or mebendazole [24-28]. These observations support the implementation of large-scale soil-transmitted helminthiases control programs that target school-age children. Side effects are rare and include mild gastrointestinal symptoms. Albendazole and mebendazole are embryotoxic and teratogenic in pregnant rats. There was a lack of risk of adverse birth outcomes after deworming pregnant women with mebendazole [29]. Nonetheless, it is recommended that treatment should be avoided during the first trimester of pregnancy [30]. Because hookworm also occurs in pregnant women, some of whom develop iron-deficiency anemia leading to adverse pregnancy outcomes, benzimidazole treatment would be beneficial during the second and third trimesters of pregnancy [31]. The WHO allows the use of benzimidazoles in children past the first year of life if the risks from adverse consequences caused by soil-transmitted helminthiases are justified [32].

2.9.2 Thiabendazole

Thiabendazole was the first anthelmintic of the benzimidazole group. It was discovered in 1964. It is active against a variety of nematodes but severe and frequent side effects limit its use [33]. Thiabendazole is absorbed rapidly after oral ingestion and reaches peak concentrations in plasma after about 1 h. Most of the drug is excreted in the urine in 24 h. Topical 15% thiabendazole in a water-soluble cream is sometimes used against cutaneous larva migrans, but ivermectin is first choice in this infection. At present, there are no helminth infections for which thiabendazole is first choice therapy. Side effects include dizzyness, nausea and vomiting, drowsiness, diarrhea, fatigue, pruritus, headache, tinnitus, convulsions, neuropsychiatric disturbances, intrahepatic cholestasis and hypersensitivity reactions including Stevens–Johnson syndrome and angioedema.

2.9.3 Mebendazole

Mebendazole was introduced in 1972. It is a benzimidazole derivative with a low systemic bioavailability of 22%. This results from a combination of poor absorption and rapid first-pass hepatic metabolism. Cimetidine will increase plasma levels of mebendazole due to inhibition of hepatic cytochrome P450-mediated metabolism [34]. Mebendazole is effective against *Ascaris*, hookworm, *Enterobius* and *Trichuris* [4]. Mebendazole is taken orally, and the same dosage schedule applies to adults and children > 2 years of age. Mass medication of groups with enterobiasis reduced symptoms rapidly, progressively and in a cost-effective way [6]. For control of ascariasis, trichuriasis or hookworm infections, 100 mg of mebendazole is taken in the morning and evening for 3 consecutive days or a single 500 mg tablet is administered once. If the patient is not cured 3 weeks after treatment, a second course should be given. A single dose of mebendazole achieves a low cure rate against hookworm and is less effective than a single dose of albendazole [4,35]. The efficacy of mebendazole against hookworm may diminish with frequent and repeated use, which may reflect emerging benzimidazole resistance [2]. Transient abdominal pain, distention and diarrhea have occurred in cases of massive infestation and expulsion of gastrointestinal worms. Rare side effects include allergic reactions, alopecia, reversible neutropenia, agranulocytosis and hypospermia. Mebendazole treatment might be associated with seizures although data are sparse [36].

2.9.4 Albendazole

Albendazole was approved in 1983. It is a benzimidazole carbamate that is variably and erratically absorbed after oral administration. A meal enhances absorption by up to fivefold [37]. Administration on an empty stomach is more appropriate when intraluminal parasites are targetted. Albendazole is rapidly oxidized in the liver and possibly in the intestine to albendazole sulfoxide (ricobendazole), an active metabolite, and then further oxidized to albendazole sulfone, which is inactive [38,39]. The plasma half-life is variable, ranging from about 4 – 15 h. It is well distributed into various tissues including hydatid cysts, in which ricobendazole reaches a concentration of about one-fifth of that in plasma [38,40]. Concentrations in cerebrospinal fluid and brain tissue are ~ 50 and 40%, respectively, of plasma levels [41]. With albendazole doses of 10 mg/(kg day), the concentration of active drug in hydatid cysts ranges from 0.52 to 1.61 mg/l [42]. In the treatment of hydatid disease,

tissue concentration of > 0.5 mg/l is required for therapeutic efficacy. Metabolites are excreted mainly in the urine. Albendazole induces its own metabolism. The elimination rate of its sulfoxide decreases by coadministration of dexamethasone and cimetidine [43,44].

Albendazole has a broad range of activity against nematodes and larvae of certain cestodes. It is also active against some protozoa, such as *Trichomonas vaginalis, Giardia lamblia* and certain microsporidia. For treatment of enterobiasis, ascariasis and hookworm, albendazole is taken as a single oral 400 mg dose by adults and children > 2 years of age. Children between the ages of 12 and 24 months take 200 mg as a single dose. Cure rates for light to moderate ascariasis are > 97%, although heavy infections may require therapy for 2 – 3 days. Three doses are preferable for trichuriasis. Albendazole is superior to mebendazole in curing hookworm and trichuriasis infections in children especially when used as a single dose [4,45]. Albendazole is effective against dog and cat hookworms that cause cutaneous larva migrans in humans, with a usual regimen of 400 – 800 mg/d (according to weight) for 3 days, and can be used when ivermectin is not available [46,47]. It can be used with success in cutaneous gnathostomiasis [48]. A dose of 400 mg twice daily for 3 days resulted in a cure rate of 75% in chronic strongyloidiasis [49]. Repeating treatment gave little extra gain. Other studies found a much lower cure rate of 38% and showed that ivermectin is clearly superior for treating this infection [50,51]. Albendazole is effective for visceral larva migrans [52], hepatic and intestinal capillariasis [53,54], and gnathostomiasis [48,55,56]. A 7 day course of 10 mg/kg twice per day was effective in clonorchiasis [57]. Its action against *Fasciola hepatica* is restricted to flukes older than 12 weeks [58]. Albendazole can be used in trichinellosis caused by several Trichinella species, usually together with prednisolone [59-62]. It is effective against *Oesophagostomum bifurcum* [8]. Topical anal albendazole application can provide early relief of pruritus ani due to enterobiasis [63].

The puncture–aspiration–injection–reaspiration technique with previous administration of albendazole is first choice for treatment of uncomplicated hepatic hydatid disease due to *Echinococcus granulosus* [64,65]. Secondary bacterial infection and connection between the cyst and the bile ducts are contra-indications. Current protoscolicidal agents include hypertonic saline, silver nitrate, cetrimide and ethanol. They are caustic for the biliary epithelium and a non-irritative agent would be welcome to limit the danger of chemical cholangitis. The use of 20% mannitol and 50% dextrose solutions is studied [66]. Surgery is more invasive and carries with it risks of operative morbidity, cyst recurrence and spillage of cyst fluid with possible consequent anaphylaxis or dissemination of infection. Albendazole reduces protoscolex and cyst viability [67]. It is used in case of accidental rupture and with puncture–aspiration–injection–reaspiration technique or surgery [68]. Albendazole by itself provides only a modest cure rate for treating cystic hydatid disease. A typical dosage regimen for adults is 400 mg given twice a day for several months. Severe disseminated hydatid disease has been successfully treated with prolonged administration of albendazole [69]. The efficacy in the treatment of pulmonary hydatid disease is variable [70,71]. Albendazole is used as adjunctive medical therapy for alveolar hydatid disease due to *Echinococcus multilocularis* [42,72-74].

The role of anthelmintics in the treatment of neurocysticercosis is controversial, as medication might induce inflammation around dying cysticerci [75]. No difference was found between albendazole and placebo in symptoms during treatment or in seizure recurrence, although albendazole plus symptomatic treatment leads to the disappearance of active cysts in 31% of the patients, compared to 7% of those with symptomatic treatment alone [76,77]. This treatment effect occurs in the first 30 days after treatment. A review of available data suggests that albendazole is more effective than praziquantel regarding clinically important outcomes in patients with neurocysticercosis [78]. However, more data are needed to confirm this [79]. The current recommended dosage is 400 mg given twice a day for adults for 8 – 30 days, depending on the number, type and location of the cysts. Pretreatment with glucocorticoids increases plasma levels of albendazole sulfoxide and reduces the incidence of neurological side effects. Therapy should include consultation with a neurologist and/or neurosurgeon regarding possible development of complications of arachnoiditis, vasculitis, cerebral edema and obstructive hydrocephalus.

Albendazole is used in the global eradication programme of lymphatic filariasis [80,81]. The combination ivermectin with albendazole proved to be superior to either drug alone in Haitian children with lymphatic filariasis, without increase in severity of adverse reactions [82]. The combination albendazole/ivermectin is used in locations in which lymphatic filariasis coexists with onchocerciasis. Such combined therapy has the extra benefit of reducing soil-transmitted helminthiases burdens in school-age children [83]. However, a Cochrane review concluded there is insufficient evidence at present to confirm or refute that albendazole co-administered with diethylcarbamazine (DEC) or ivermectin is more effective than DEC or ivermectin alone in clearing microfilariae or killing adult worms [84]. GlaxoSmithKline produces albendazole and donates the drug for lymphatic filariasis control programs. Albendazole may be useful for the treatment of loiasis when DEC is ineffective or cannot be used [85].

Albendazole is well tolerated by most patients [86]. Side effects of albendazole include abdominal pain, nausea, vomiting, headaches, fever, fatigue, loss of hair, allergic reactions, leukopenia and thrombocytopenia. Increased hepatic transaminases are usually transient and do not require discontinuation of the drug. Serious adverse drug reactions to albendazole most often occurred when the drug was used for the treatment of echinococcosis, when high dosage and long duration of therapy were required [87]. Liver

function tests should be monitored during long-term albendazole therapy.

2.9.5 *Triclabendazole*

Triclabendazole is a benzimidazole derivative that has been used since 1983 in veterinary medicine. It is rapidly oxidized into two active metabolites, triclabendazole sulfoxide and triclabendazole sulfone. Administration with food is recommended [88]. Fascioliasis has no significant effect on the pharmacokinetic parameters of the orally administered triclabendazole [89]. It has no activity against nematodes. Triclabendazole has weak and inconsistent schistosomicidal activities [90]. The range of activity suggests a mechanism of action unlike that of other benzimidazole anthelmintics. In 1986, triclabendazole was administered first to two human patients with fasciolasis. It became the drug of choice for treating fascioliasis as it is active against adult worms and immature stages of *F. hepatica* [91-93]. Since 1997, triclabendazole has been included in the WHO essential drugs list. A single postprandial dose of triclabendazole 10 mg/kg for the treatment of human fasciolasis is recommended. In severe cases, a second or even third treatment cycle is needed [94]. Cure rate at 2 months was 94% when assessed by the disappearance of eggs in stools and 88% when assessed by both the absence of eggs in stools and of worms in the biliary system. The split dose was slower in action but slightly more efficacious. Triclabendazole-resistant *Fasciola* was first reported in 1995 in Australia, and later in Ireland, Scotland, Wales, Spain and The Netherlands [95]. Parallel to the spread of resistance there has been a sharp increase in the prevalence of fascioliasis. Triclabendazole-resistant *F. hepatica* strains have not yet been isolated from humans. An altered influx/efflux mechanism may account for the development of resistance to triclabendazole [96]. The reliance on a single drug puts treatment strategies for fascioliasis at risk as no other drug possesses such high activity against the immature stages of the fluke [92,95]. The drug is promising as an alternative to praziquantel in the treatment of paragonimiasis [97-99]. Side effects tend to be minor [100].

2.10 Diethylcarbamazine

DEC is a substituted piperazine derivative and was first reported to have filaricidal effect in 1947. It is formulated as the tasteless, odourless and heat-stable water-soluble citrate salt containing 51% by weight of the active base. The compound can be taken in the form of fortified table salt containing 0.2 – 0.4% by weight of the base [101]. DEC is absorbed rapidly from the gastrointestinal tract. Peak plasma levels occur in 1 – 2 h after a single oral dose. The plasma half-life varies from 2 to 10 h, depending on the urinary pH. The major metabolite DEC-N-oxide is active. More than 50% of an oral dose appears in acidic urine as the unchanged drug. Alkalinizing the urine can elevate plasma levels, prolong the plasma half-life and increase both the therapeutic effect and toxicity of DEC [102]. Dosage reduction may be required for people with renal dysfunction or sustained alkaline urine.

DEC is the drug of choice against lymphatic filariasis due to infection with *Wuchereria bancrofti, Brugia malayi* and *B. timori* and for tropical pulmonary eosinophilia (Weingarten syndrome). The mechanism of action of DEC on susceptible microfilariae is not well understood, but interference with arachidonic acid metabolism is possible. It is also possible that the piperazine moity present in DEC exerts a hyperpolarizing effect. A direct effect on *W. bancrofti* microfilariae including loss of sheath, organelle damage and apoptosis was described [103]. It is microfilaricidal *in vivo*, but does not affect the microfilariae of *W. bancrofti* in a hydrocele, despite penetration into the fluid. The standard regimen for the treatment of symptomatic lymphatic filariasis is 12-day, 72 mg/kg (6 mg/(kg day)) course of DEC. A single dose of 6 mg/kg has comparable microfilaricidal efficacy to the standard regimen [81]. Drug combinations containing DEC were the most effective against microfilarial prevalence and intensity relative to single drugs or other combinations [104]. DEC does not reverse existing lymphatic damage, but may prevent new lymphatic damage. Repeat treatment is recommended if microfilariae remain in the circulation or if adult worms remain motile on scrotal ultrasound. During acute episodes of lymphangitis, treatment with DEC is not recommended until acute symptoms subside. Side effects are generally proportional to the microfilarial burden. The clinical and histological features of the reaction are consistent with allergic responses to parasite products. Side effects are also to an extent attributable to release of lipopolysaccharides and other constituents from endosymbiontic *Wolbachia* bacteria [105,106]. These include fever, headache, dizziness and transient exacerbation of lymphangitis. Supportive treatment is essential for the management of lymphatic filariasis, including prevention of erysipelas and other secondary bacterial infections. Attention to hygiene, wearing shoes to prevent foot injury and avoidance of lymphostasis through exercise and limb elevation are important. A retrospective cohort study of 57 men whose adult *W. bancrofti* were not sensitive to DEC was published [107]. Survival of adult *W. bancrofti* is inversely associated with transmission intensity. It is unclear at present what implications these findings have for filariasis elimination programs.

DEC is first choice for therapy of loiasis. Treatment is initiated with doses of 50 mg (1 mg/kg in children) daily for 2 – 3 days, gradually increasing the dose to 400 mg/day for 2 – 3 weeks. Pretreatment with antihistamines or glucosteroids diminish reactions to dying microfilariae and adult worms. Repeated courses of DEC may be required for complete cure. The drug occasionally induces encephalopathy in severe loasis [108]. Patients with very high microfilariemias can initially be treated with exchange blood transfusion or apheresis [109]. DEC is clinically effective against microfilariae and adult worms of *Dipetalonema streptocerca*, but not for filariasis due to *Mansonella perstans*. It is obsolete for

the treatment of onchocerciasis since the development of ivermectin. DEC should not be used anymore for onchocerciasis as severe side reactions can lead to optic nerve inflammation, visual loss and blindness. DEC can be used for visceral larva migrans (toxocariasis), but albendazole is used more often [110,111].

Toxic reactions to DEC are rarely severe and usually disappear in a few days despite continuation of therapy. Such reactions include anorexia, nausea, headache and vomiting. Major adverse effects result directly or indirectly from the host response to destruction of parasites, primarily microfilariae. Pretreatment with glucocorticoids and antihistamines often is undertaken to minimize indirect reactions to DEC that result from dying microfilariae. In patients with onchocerciasis, DEC provokes the Mazzotti reaction that occurs in a few hours after the first dose and includes intense itching, enlargement and tenderness of the lymph nodes, and sometimes a popular rash, fever, tachycardia, arthalgias and headache. Ocular complications include limbitis, punctuate keratitis, uveitis and atrophy of the retinal pigment epithelium. In patients with bancroftian or brugian filariasis, nodular swellings may occur along the course of the lymphatics, and there often is an accompanying lymphadenitis. This reaction also subsides in a few days. Leukocytosis and a temporary eosinophilia are common in the first couple of days after starting DEC. Reversible proteinuria may occur. DEC seems to be safe for use during pregnancy.

2.11 Ivermectin

In the 1970s, the actinomycete *Streptomyces avermitilis* (later renamed *S. avermectinius*) was isolated from soil near an oceanside golf course in Kanawa, Japan [112]. The fermentation products had potent anthelmintic activity. The active compounds are a mixture of eight related 16-membered macrocyclic lactones. Reduction of the C22–C23 double bond of avermectin B1a and avermectin B1b results in 22,23-dihydro B1 complex. Ivermectin is a mixture of 80% avermectin B1a and 20% avermectin B1b [113]. Ivermectin prevents closure of glutamate-gated chloride channels in nerve and muscle cells [114]. This leads to hyperpolarization and paralysis of the somatic muscles, especially those of the pharyngeal pump. In vertebrates, it can stimulate the release of GABA in CNS neurons, but these are protected by the blood–brain barrier. Ivermectin is active against a diverse range of nematodes, insects, mites and ticks. Lack of high-affinity avermectin receptors in cestodes and trematodes may explain why these helminths are not sensitive to ivermectin. Peak levels of ivermectin in plasma are achieved in 4 – 5 h after oral administration. The terminal half-life in adults is 57 h. Cytochrome P4503A4 metabolizes ivermectin in human liver microsomes to at least 10 metabolites [115]. Lactating women taking the drug secrete low levels in their milk. It is likely that a P-glycoprotein efflux pump in the blood–brain barrier prevents ivermectin from entering the CNS. This and the limited affinity of ivermectin for CNS receptors may explain the paucity of CNS side effects and the relative safety of this drug in humans.

The avermectins proved to be hugely succesful in veterinary medicine. Because of its activity against the horse nematode, *Onchocerca cervicalis*, it was evaluated for use in human onchocerciasis. In 1981, clinical trials for treatment of human onchocerciasis began in Senegal. A single annual dose of 200 μg/kg of body weigth reduces the levels of skin microfilaria by 96 – 99% in the first few months [116]. Ivermectin has little impact on the adult worms and is, therefore, suppressive rather than curative. Suppression of *Onchocerca volvulus* microfilaridermia lasts about 1 year. How this is achieved is not clear. By reducing microfilariae in the skin, ivermectin decreases transmission to the *Simulium* black fly vector. Ivermectin therapy results in reversal of lymphadenopathy and acute inflammatory changes in ocular tissues and arrests the development of further ocular pathology due to microfilariae. In 1987 it was approved for human use. After consent from the Kitasato Institute, which agreed to forego royalties, the pharmaceutical company MSD announced that ivermectin would be provided free of charge for the treatment of onchocerciasis for as long as it would be needed. This donation dramatically improved the prospects for the eradication of onchocerciasis. Mass drug administrations began in 1988. In the 1990s, the Onchocerciasis Elimination Program in the Americas and the African Program of Onchocerciasis Control were created with the goal to eliminate onchocerciasis as a public health problem. Elimination is the objective of the Onchocerciasis Elimination Program in the Americas because studies in Guatemala and Ecuador indicate that elimination can be achieved. However, control remains the objective of the African programs. Since 1987 > 570 million cumulative treatments were provided [117].

In lymphatic filariasis, ivermectin leads to clearance of microfilariae of *W. bancrofti* and *B. malayi* from the blood, but it is not active against adults. By annual dosing with combination therapy for 4 – 6 years, the strategy is to maintain the microfilaremia at such low levels that transmission cannot occur. This period corresponds to the estimated duration of fecundity of adult females. Combinations of ivermectin and albendazole or ivermectin and DEC have been adopted as the basis of mass treatment on the Global Alliance to Eliminate Lymphatic Filariasis, which was initiated by WHO in 1997. Unlike DEC, ivermectin can be used in regions where onchocerciasis, loiasis or both infections are endemic. Merck & Co. donates ivermectin free of charge to elimination programs in regions where onchocerciasis and lymphatic filariasis coexist.

Ivermectin temporary decreases microfilaremia in loasis [118]. *Loa* encephalopathy is associated with ivermectin treatment of individuals with very high microfilaremia. Most of the cases of *Loa* encephalopathy in association with ivermectin chemotherapy have been recorded in central Cameroon [119].

Ivermectin is effective against *Mansonella ozzardi* [120]. A single dose of 600 µg/kg is not active against *M. perstans* [121].

Ivermectin is effective against *Ascaris*, *Trichuris* and *Enterobius* [122]. A single 200 µg/kg oral dose is efficient for treatment of cutaneous larva migrans caused by dog or cat hookworms [123]. It is ineffective against human hookworm [122]. A single dose of 100 µg/kg of ivermectin is as effective as treatment of intestinal strongyloidiasis with thiabendazole, and less toxic [124]. In a Phase III trial in Japan, 49 of 50 *Strongyloides stercoralis*-infected patients were cured after they received 200 µg/kg of ivermectin orally twice at an interval of 2 weeks [114]. Similar high cure rates were obtained with two doses of 200 µg/kg given 2 weeks apart [125]. In one comparative study, ivermectin (150 – 200 µg/kg as a single oral dose) was superior to albendazole (400 mg/d for 3 days) for the treatment of strongyloidiasis with 83 versus 38% cured [51]. For refractory strongyloidiasis or therapy in patient with underlying immunodeficiencies, including human T-lymphotropic virus I infections, treatment should be repeated at 2 weeks [126]. Multi-dose ivermectin therapy has also proved necessary and effective for hyperinfection with *S. stercoralis* in patients with AIDS [127]. A single dose ivermectin (200 µg/kg) seems less effective than prolonged albendazole (400 mg/day for 21 days) for the treatment of cutaneous gnathostomiasis [128]. When the same dose was given on two consecutive days, a cure rate of 100% was achieved [56]. Rectal administration of ivermectin effectively treated hyperinfection strongyloidiasis in one renal transplant recipient whose strongyloidiasis was complicated by paralytic ileus [129].

Ivermectin is effective in treating certain human ectoparasites. For scabies, ivermectin is given at 200 µg/kg orally twice at a 2-week interval and can be useful in community or institutional outbreaks [130]. Similar doses are effective against human lice [131,132].

Most adverse effects are mild and transient. The side effects of ivermectin therapy of onchocerciasis include pruritus, papular rash, dizziness, facial and limb edema, and rarely ocular inflammation. These represent reactions to dying microfilariae and their release of proinflammatory constituents by endosymbiontic *Wolbachia* bacteria [105]. These reactions are significantly less severe and less frequent than those induced by DEC [133]. No significant adverse effects have been observed in women inadvertently treated during pregnancy [134]. A review of serious adverse effects following ivermectin treatment of onchocerciasis was carried out in 1989 – 2001 and found 207 cases from a reported 165 million treatments [135]. Because of its effects on GABA receptors in the CNS, ivermectin is contraindicated in conditions associated with an impaired blood–brain barrier (e.g., human African trypanosomiasis and meningitis). Caution also is advised about coadministration of ivermectin with other agents that depress CNS activity. Epileptics should not be excluded from onchocerciasis treatment programs unless actively seizing or postictal [136].

Ivermectin resistance has been described in trichostrongylid nematodes of ruminants. The basis for resistance or relative unresponsiveness by different nematodes is complex. The extact mechanism is still a matter of debate. Resistance could be mediated by mutations in the subunits of the glutamate-gated chloride channels. The β-tubulin and P-glycoprotein genes may prove useful for monitoring for possible development of ivermectin resistance [137,138]. When ivermectin is used in large-scale programs against onchocerciasis as a single drug over many years, decreasing susceptibility or overt resistance might develop (definition of resistance is a bit tricky as ivermectin is not macrofilaricidal). Finding patients with high microfilarial counts despite several rounds of ivermectin treatment suggests suboptimal response or even resistance [139,140]. The spread of resistant macrofilariae could lead to recrudescence of the disease.

2.12 Praziquantel

Praziquantel was identified in 1972. It is a racemate of isoquinoline derivatives. The (R)-enantiomer is responsible for anthelmintic activity. It is also active against intestinal tapeworms, cysticercosis and most flukes. *Fasciola hepatica* and nematodes are unaffected. Praziquantel should be stored at temperatures below 30°C and swallowed with water without chewing because of its bitter taste. Praziquantel is readily absorbed after oral administration. Extensive first-pass limits bioavailability and results in plasma concentrations of inactive metabolites at least a 100-fold higher than that of praziquantel. Maximal plasma levels occur 1 – 2 h after ingestion and are higher with a carbohydrate diet. Its plasma half-life is 0.8 – 3 h, depending on the dose, compared with 4 – 6 h for its metabolites. It may be prolonged in patients with severe liver disease. Praziquantel permeates the blood–brain barrier, which is important in neurocysticercosis. Bioavailability of the drug is reduced when given jointly with carbamazepine, phenytoin or dexamethasone [141]. Coadministration of cimetidine has the opposite effect [142].

Praziquantel is the drug of choice for treating schistosomiasis caused by all *Schistosoma* species that infect humans [143]. As it is active against adult stages of the parasite, it is less than optimal in acute schistosomiasis (Katayama fever) [144,145]. Katayama fever is considered to be caused (generally in non-endemic populations) by inflammatory reactions starting at the time of egg-laying, for which steroids are the most effective treatment. Praziquantel causes an influx of Ca^{2+} across the tegument. This results in spastic paralysis and tegumental disruption. Whether or not host immune status is important for clinical efficacy of praziquantel in humans is debated. Dosage regimens vary: a single oral dose of 40 mg/kg or three doses of 20 mg/kg each, given 4 – 6 h apart, generally produce cure rates of 70 – 95% and consistently high reductions (> 85%) in egg counts. Decreased clinical efficacy of praziquantel against infections with *S. mansoni* has been reported in an area of high transmission and high

worm burden in northern Senegal [146]. In Egypt several isolates showed diminished sensitivity [147]. A polymerase chain reaction has been developed to distinguish resistant from sensitive Egyptian strains of *S. mansoni* [148]. Praziquantel therapy in a daily dose of 25 mg/kg for 2 days achieved a cure rate of 52% for clonorchiasis in Vietnam [149]. In a Korean Phase II study of clonorchiasis, a single sustained-release praziquantel tablet (30 mg/kg) achieved a cure rate of 60% and a 95.5% egg reduction rate [150]. Praziquantel is highly effective against *Paragonimus westermani* [151]. Low doses of praziquantel are used to treat intestinal infections with adult cestodes, for example, a single oral dose of 25 mg/kg for *H. nana* and 10 – 20 mg/kg for *D. latum, T. saginata* or *T. solium* [17]. Retreatment after 7 – 10 days is advisable for infections with *H. nana*. Although albendazole under steroid cover is generally preferred for therapy of human cysticercosis, praziquantel remains an alternative treatment [75,79]. The use of single day praziquantel has been described with good results for single lesions, but not for multiple brain cysts [152]. Shortly after taking the drug, driving, operating machinery and other tasks requiring mental alertness should be avoided. Side effects include headache, dizziness, drowsiness, abdominal discomfort, pain, nausea and diarrhea. These symptoms are transient and dose-related. Fever, pruritus, urticaria, rashes, arthralgia and myalgia are noted occasionally. Such side effects and increases in eosinophilia often relate to parasite burden. Praziquantel is safe during pregnancy [153,154].

2.13 Nitazoxanide

Nitazoxanide is a nitrothiazole derivative, chemically related to niclosamide. It has excellent bioavailability when taken orally [155,156]. It is a prodrug that is metabolized to the main active metabolite, tizoxanide. A second metabolite, tizoxanide glucoronide is inactive. Nitazoxanide does not inhibit cytochrome P450 enzymes. Therefore, no drug interactions are expected with agents that are metabolized or inhibited by cytochrome P450 enzymes. Nitazoxanide is active against a number of helminths, protozoa (including cryptosporidia and *Giardia*), anaerobic bacteria and even against hepatitis C virus [155,157,158]. It also exhibits anti-inflammatory properties, prompting clinical investigations for its use in Crohn's disease [158]. It is likely that different mechanisms of action act on intracellular versus extracellular pathogens.

Three randomized clinical studies were conducted in 2000 to evaluate the efficacy of nitazoxanide pediatric suspension compared to albendazole in the treatment of ascariasis and trichuriasis, and praziquantel in the treatment of hymenolepiasis in Peruvian children [159]. Nitazoxanide was administered at a dose of 100 mg (age 1 – 3 years) or 200 mg (age 4 – 11 years) twice daily for 3 days, albendazole as a 400 mg single dose and praziquantel as a 25 mg/kg single dose. Nitazoxanide cured 89, 89 and 82% of the cases of ascariasis, trichuriasis and hymenolepiasis, respectively, compared with 91, 58 and 96% for the comparator drugs. Each of the drugs produced egg reduction rates in excess of 98%. Another Peruvian study of hymenolepiasis showed a treatment efficacy of 75% [160]. A single 25 mg/kg body weight dose was effective against *T. saginata*, whereas twice this dose was required for hymenolepiasis [161]. Niclosamide- and praziquantel-resistant beef tapeworm can be treated successfully with nitazoxanide [162]. Nitazoxanide in combination with albendazole might be useful for treatment of cysticercosis and echinococcosis, but more research is required [163,164]. A 7-day course of nitazoxanide eliminated *F. hepatica* in 60% of patients [165]. Adverse effects tend to be rare and mild. They include abdominal pain, headache, skin rash of moderate severity, diarrhea and nausea.

2.14 Antibiotics

Many filarial parasites, including *W. bancrofti* and *O. volvulus*, harbor bacterial symbionts of the genus *Wolbachia* [166]. The worms depend on these endosymbionts for normal metabolism and reproduction. A 6-week regimen of doxycycline of 100 mg daily resulted in bacterial depletion, sterility of adult female *Onchocerca*, and was macrofilaricidal [167]. Azithromycin administered alone for 6 weeks at 250 mg/day or 1200 mg/week is not suitable for treatment of human onchocerciasis [168]. Rifampicin might be an alternative for onchocerciasis cases that cannot be treated with doxycycline [169]. Doxycycline also proved active in *W. bancrofti* infections [170]. Inflammatory reactions to antifilarial treatment are related to the number of microfilariae and *Wolbachia* endosymbionts released into plasma [171]. Doxycycline might be developed as second-line drug for onchocerciasis, to be administered in areas without transmission, in focus with ivermectin resistance and in areas with *Loa* co-infections [167]. Side effects include photodermatitis, photo-onycholysis and mucosal candidiasis.

2.15 Artemisinin derivatives

The Chinese plant *Artemisia annua* is the source of artemisinin. Semisynthetic derivatives include artesunate and artemether. These are sesquiterpene lactones with a peroxide bridge. Full chemical synthesis was reported in 1983, but is very expensive. Efforts to achieve synthesis through genetic recombinant engineering are under way. After oral administration there is an important first-pass effect in the liver. The plasma half-life of artemether is only 1 h. The products are rapidly converted after ingestion to the active dihydro-artemisinin. Inhibitors of cytochrome P450 such as grapefruit juice can double the plasma levels of artemether. Artemisinin is eliminated by glucuronidation to inactive metabolites. Artemisinins increase their own clearance. Artemisinin derivates have been mainly studied for their antimalaria activity, and form the backbone of the artemisinin-based combination treatment strategy for this illness.

There are arguments to limit the use of artemisinin derivatives to malaria treatment. However, they also have antitrematode activity. High worm-burden reductions were obtained with these drugs in rodents with acute

or chronic infections of *S. japonicum, S. mansoni, Clonorchis sinensis, F. hepatica* and *Opisthorchis viverrini*. Artemether exhibits the highest activity against juvenile stages of the parasites, whereas adult worms are significantly less susceptible [172]. A randomized controlled trial in a *Schistosoma japonicum* endemic area of southern China enrolled 783 individuals [173]. After taking a single oral dose of praziquantel (50 mg/kg), they were randomly assigned oral artemether (6 mg/kg) or placebo, administered once every 2 weeks for 9 – 11 doses, covering the entire transmission season for *S. japonicum*. Stool examination 1 month after the final dosing revealed eggs of *S. japonicum* in 0.8% of the artemether recipients versus 15.0% in placebo recipients ($p < 0.001$). The geometric mean intensity of the infection had decreased by 96.1% in the artemether group and increased by 50.8% in the placebo group. No acute schistosomiasis cases were observed in the artemether group, whereas three such cases were reported from the placebo group. Oral artemether produced no drug-related adverse effects. Promising results were obtained in a small group of patients with *Plasmodium falciparum* and *S. mansoni* co-infection treated with artesunate–sulfamethoxypyrazine–pyrimethamine or with artemether–lumefantrine [174]. When checked a month after initiation of treatment, all patients were found stool-negative for schistosome eggs. Comparable beneficial effects were seen in children with malaria and *S. haematobium* infection who received artesunate combination treatment, resulting in a *S. haematobium* cure rate of 92% [175]. In a double-blind, randomized, placebo-controlled study of artesunate and praziquantel for the treatment of *S. haematobium*, the praziquantel plus placebo-treated group attained a cure rate of 73%, artesunate plus placebo a rate of 27%, the combination of artesunate and praziquantel a rate of 81%, and placebo alone a rate of 20% [176]. The efficacy of artemisinin derivitives against *S. mansoni* and *S. japonicum* could not be confirmed in *S. haematobium* infections in this study. The activity of artemisinins in schistosomiasis has been recently reviewed [177]. Artemether integrated with other control strategies has potential for reducing the current burden of schistosomiasis. There is a theoretical risk that such treatment might select for resistance, not only in schistosomes, but also in plasmodia. There may be a role for artesunate and artemether in fascioliasis [178,179].

2.16 Tribendimidine

Tribendimidine is a symmetrical diamidine derivative of amidantel. It was developed in Shangai, China and was approved by Chinese authorities for human use in 2004. Single oral doses of tribendimidine (300 mg) and albendazole (400 mg) were equally effective against *Ascaris lumbricoides* infection [180]. In 5 – 14 year old children with enterobiasis, treated with a single oral dose of 200 mg tribendimidine, a cure rate of 81.6% was observed. A single oral dose of 400 mg tribendimidine, administered to patients infected only with *Necator americanus*, or with *N. americanus* and *Ancylostoma duodenalis*, resulted in cure rates of 85.7 and 89.8%, respectively, significantly higher than those achieved with a single oral dose of 400 mg albendazole [180]. Another open clinical trial of 1292 infected persons studied the effect of tribendimidine enteric-coated tablets for a number of intestinal helminths [181]. Patients with ascariasis received a single dose of 300 mg, whereas patients with *A. duodenale*, mixed *A. duodenale* and *A. lumbricoides*, or with other helminth infections, took a single dose of 400 mg. The cure rate of the patients with ancylostomiasis was 88%, whereas in patients with ascariasis, cure rate was 95.0%. The cure rate of patients with trichuriasis at a single dose of 400 mg was 76.8%. Animal studies suggest it is active against *C. sinensis* and *O. viverrini*, but inactive against *S. mansoni*, paragonimiasis or *F. hepatica* disease [182-185]. Tribendimidine exhibits activity against *Strongyloides ratti* in vitro and in vivo [186]. An open-label randomized trial showed that a single-dose has significant activity against *S. stercoralis* and *Taenia* sp [187]. Multiple-dose schedules should be evaluated. Tribendimidine seems to be well-tolerated as only mild and transient side effects were observed.

2.17 Myrrh

Myrrh (Mirazid) is an oleo-gum resin from the stem of the plant *Commiphora molmol*. It has been produced and marketed as an antischistosomal drug since 2001. An initial study showed a high cure-rate of 98% [188]. A randomized clinical trial in which praziquantel was compared with myrrh in *S. mansoni*-infected Egyptian patients was disappointing with a cure rate of < 20% [189]. Another randomized trial also compared myrrh with praziquantel and found similar very low cure rates (< 10%) for myrrh [190]. The results raise serious doubts about the antischistosomal properties of myrrh. At present myrrh cannot be recommended as an agent to control schistosomiasis. In an Egyptian study of fascioliasis all patients were treated with two capsules (600 mg) on an empty stomach an hour before breakfast for six consecutive days [191]. The parasitological cure rates 2 and 3 months after treatment were 88.2 and 94.1% with overt clinical cure without any side effects. These encouraging data need confirmation.

2.18 Possible future anthelmintics

2.18.1 Cyclic octadepsipeptides

Research on cyclic octadepsipeptides started in the 1990s. Emodepside is a semisynthetic derivative of PF1022A, a secondary metabolite of the fungus *Mycelia sterilia*, which belongs to the microflora of the leaves of *Camellia japonica* [192,193]. The anthelmintic activity is directed against gastrointestinal nematodes in chicken, mice, rats, dogs, cats, sheep, cattle and horses, as well as *Trichinella spiralis* larvae in muscles [194]. Emodepside induces flaccid paralysis of the pharynx and the somatic musculature. It is possible that emodepside exerts its action on nematode muscles and neurons through interference with a calcium-activated

potassium channel and through a presynaptic latrophilin-like receptor [192,195,196]. Emodepside and PF1022A are effective against benzimidazole-, levamisole- or ivermectin-resistant nematodes in sheep and cattle [194]. Murine tests suggest that PF1022A would be a promising candidate drug in treating abdominal and cerebral angiostrongyliasis [197]. It is not clear at this moment if these compounds will find a place in human therapeutics.

2.18.2 Moxidectin

Moxidectin is a milbemycine used as a veterinary antiparasitic agent in companion and farm animals. It is chemically related to ivermectin, and acts as a neurotoxin on glutamate-gated chloride ion channels. Safety assessments in human volunteers suggest that moxidectin was safe and well tolerated between doses of 3 and 36 mg, with a slightly higher incidence of transient, mild and moderate CNS as the dose increased as compared to placebo [198]. The mean elimination half-life was 20 – 35 days. A high-fat breakfast delayed and increased the overall absorption but did not increase maximal concentrations when compared to administration in the fasted state. It was promising in a mouse model of onchocerciasis [199]. Clinical studies will have to determine the eventual therapeutic place, if any, of this compound.

2.18.3 Trioxolane OZ78

The synthetic trioxolane OZ78 is active against a number of trematodes, including *C. sinensis*, *O. viverrini*, triclabendazole-resistant *F. hepatica* and schistosomes [200-205]. Rats infected with *C. sinensis* for 2 and 5 weeks were treated orally with single doses of OZ78 (75, 150 or 300 mg/kg). Worm burden reductions were assessed against untreated control rats. A single 300 mg/kg oral dose of OZ78 resulted in worm burden reductions of 78.5 and 98.5% against juvenile and adult *C. sinensis*, respectively. Scanning electron microscopy revealed tegumental surface alterations, including blebbing and sloughing. It remains to be determined if this trioxolane or related drugs will gain a place in the therapeutic arsenal for worm infections.

2.18.4 Nafuredin

Nafuredin is a δ-lactone antibiotic. This fungal metabolite was obtained from culture broth of *Aspergillus niger* isolated from a marine sponge [206]. Nafuredin inhibits NADH-fumarate reductase, a unique anaerobic electron transport system, in helminth mitochondria. It exerts anthelmintic activity against *Haemonchus contortus* in sheep. Further evaluation is needed.

2.18.5 Furoxan

Furoxans belong to a class of oxidiazole derivatives. One compound of this class, 4-phenyl-3-furoxancarbonitrile inhibits schistosomal thioredoxin–glutathione reductase. This enzyme is central in the defense against reactive oxygen species produced by the host's innate immune response [207]. This enzyme is also inhibited by potassium tartrate and oltipraz, two previously used antischistosomal compounds. It was identified as a lead compound in quantitative high-throughput screening based on the activity of the *S. mansoni* redox pathway [208]. Furoxan is effective against all developmental stages of *S. mansoni*, which is an advantage over praziquantel. It is also active against adults of *S. japonicum* and *S. haematobium*.

3. Conclusion

Albendazole, praziquantel and ivermectin are the most important anthelmintics available, easy to use and active against most helminths. Single dose oral albendazole, mebendazole and pyrantel pamoate show a high cure rate against *A. lumbricoides*. For hookworm, albendazole is first choice. Treatment of *Trichuris trichiura* with single oral doses of current anthelmintics is unsatisfactory [4]. Ivermectin is first choice in strongyloidasis, cutaneous larva migrans and onchocerciasis. Praziquantel is the drug of choice for intestinal cestodes, schistosomiasis and other trematodiases except fascioliasis. DEC has an important role in loasis and lymphatic filariasis. Triclabendazole is a welcome addition and is first choice in fascioliasis. Tribendimidine and nitazoxanide are promising leads. Artemisinine derivatives have antischistosome activity, and are studied for anti-*Fasciola* and anti-*Echinococcus* activity, but their eventual place in therapy or prevention needs to be further defined. Doxycycline can eliminate endosymbiotic *Wolbachia* bacteria of certain filariae. A better, non-caustic protoscolicidal drug would diminish the complication rate of cystic hydatid disease treatment.

4. Expert opinion

Most helminths cannot be cultured (yet) in continuous culture. The absence of a suitable culture system is a major impediment to research into the basic biology of these organisms and the effects of drugs on them. *Caenorhabditis elegans* provides a valuable model for research on the basic pharmacology of anthelmintic drugs. A disadvantage is the profound difference in lifestyle of this nematode compared with a parasite in a host. The number of available anthelmintics is limited. There has been little investment in the development of new anthelmintics for humans, as the drugs would mainly be used in poorer countries, resulting in little financial incentives for commercial companies. Nearly all anthelmintics have been developed first for veterinary use. The number of known biological targets of the current anthelmintics is limited. In the coming decade, quantitative high-throughput screening, progress in etnobotany and the analysis of helminth genomes and techniques such as RNAi are expected to facilitate the discovery of new drug targets and new anthelmintics [208,209]. It has been stated that "first-line treatments are currently so reliable that failure should lead first to investigation

of possible false failure causes" [210]. Still, in view of the worrying history of development of drug resistance in livestock, there is concern about development of resistance in human helminths. However, there is no widely accepted definition of resistance for helminth infections yet [211]. Reduced drug efficacy might be owing to other factors, such as poor compliance, absorption problems, inability to metabolize a particular drug and/or new infections. In the absence of genotypic screening assays for determining the frequency of resistance alleles, detection of resistance relies on changes in cure rates and egg reduction rates. However, there is a lack of standard procedure for monitoring drug efficacy. There is wide variation in the timing and type of diagnostic test used to evaluate parasitological cure or egg reduction rates. This contributes to the heterogeneity between study results. Geographical location also seems to have influence on cure rates [212]. To delay the development of drug resistance, it is advised to give priority to accessible diagnosis and treatment of symptomatic individual cases, using the correct dose, avoid indiscriminate mass treatment, and increase programs of health education and sanitation. It is likely that development of drug resistance is delayed if drugs with a different working mechanism are used in combination. Treatment is usually limited to individual patients or target groups such as school-age children (as opposed to indiscriminate mass treatment) who often have a compliance of < 80%. Single-dose schemes are not optimal and infections often require several treatment rounds. People who are not treated during campaigns form passive refugia, where a part of the worm population is not exposed to drugs and thus escapes selection pressure for resistance [213]. The use of lower drug doses might select for resistance. There is an urgent need to develop new anthelmintics, evaluation of drug combinations, as well as novel non-chemical approaches for parasite control (e.g., vaccines) and practical molecular assays capable of detecting and monitoring drug resistance. Existing drugs for others condition need to be re-evaluated for eventual anthelmintic properties. A multivalent anthelmintic vaccine to prevent hookworm and schistosomiasis might become a reality [214,215]. Anthelmintic treatment definitely has health benefits, but in our focus on pathogenic worms, we might forget to look for unanticipated effects. Other partially answered questions include how the battle against helminths will influence the manifestations of other diseases, such as malaria, inflammatory bowel disease or atopy [216-219]. More study is needed, not only to develop extra anthelmintics and vaccines or detect resistance, but also to understand fundamental aspects of these diseases.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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