International Journal for Parasitology: Drugs and Drug Resistance 4 (2014) 185–200

Contents lists available at ScienceDirect

International Journal for Parasitology: Drugs and Drug Resistance

journal homepage: www.elsevier.com/locate/ijpddr

Invited Review

Repurposing drugs for the treatment and control of helminth infections

Gordana Panic, Urs Duthaler, Benjamin Speich, Jennifer Keiser *

Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, Basel, Switzerland
University of Basel, P.O. Box, CH-4003 Basel, Switzerland

ARTICLE INFO

Article history:
Received 16 April 2014
Received in revised form 4 July 2014
Accepted 13 July 2014
Available online 30 July 2014

Keywords:
Drug repurposing
Drug repositioning
Helminths
Anthelmintic
Schistosoma
Trematodes
Soil-transmitted helminths
Cestodes

ABSTRACT

Helminth infections are responsible for a considerable public health burden, yet the current drug armamentarium is small. Given the high cost of drug discovery and development, the high failure rates and the long duration to develop novel treatments, drug repurposing circumvents these obstacles by finding new uses for compounds other than those they were initially intended to treat. In the present review, we summarize *in vivo* and clinical trial findings testing clinical candidates and marketed drugs against schistosomes, food-borne trematodes, soil-transmitted helminths, *Strongyloides stercoralis*, the major human filariases lymphatic filariasis and onchocerciasis, taeniasis, neurocysticercosis and echinococcosis. While expanding the applications of broad-spectrum or veterinary anthelmintics continues to fuel alternative treatment options, antimalarials, antibiotics, antiprotozoals and anticancer agents appear to be producing fruitful results as well. The trematodes and nematodes continue to be most investigated, while cestodal drug discovery will need to be accelerated. The most clinically advanced drug candidates include the artemisinins and mefloquine against schistosomiasis, tribendimidine against liver flukes, oxantel pamoate against trichuriasis, and doxycycline against filariasis. Preclinical studies indicate a handful of promising future candidates, and are beginning to elucidate the broad-spectrum activity of some currently used anthelmintics. Challenges and opportunities are further discussed.
© 2014 The Authors. Published by Elsevier Ltd. on behalf of Australian Society for Parasitology Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Contents

* Corresponding author. Address: Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, P.O. Box, CH-4002 Basel, Switzerland. Tel.: +41 61 284 8218; fax: +41 61 284 8105.
E-mail address: jennifer.keiser@unibas.ch (J. Keiser).

http://dx.doi.org/10.1016/j.ijpddr.2014.07.002
2211-3207/© 2014 The Authors. Published by Elsevier Ltd. on behalf of Australian Society for Parasitology Inc.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

1. Introduction

Helminth infections caused by roundworms (nematodes) and flatworms (platyhelminths) comprise the greatest group of the neglected tropical diseases (NTDs) (Hotez et al., 2006). An estimated 11.5 million disability adjusted life years (DALYs) are attributed to intestinal nematode infections, schistosomiasis, lymphatic filariasis, onchocerciasis, food-borne trematodiasis, cysticercosis and echinococcosis (Murray et al., 2012). Most of the burden of these diseases results from disability (rather than premature death), influencing school attendance, child development and overall economic productivity, thus resulting in disease driven poverty traps (Hotez et al., 2006). In a recent special issue of the Disease Clinics of North America (Zumla and Keiser, 2012), cestode infestations (Brunetti and White, 2012), schistosomiasis (Gryseels, 2012), food-borne trematodiases (Fürst et al., 2012), filariases (Knopp et al., 2012a) and soil-transmitted helminthiases (Knopp et al., 2012b) were presented in great detail and hence for background information on these diseases, the reader is referred to these excellent publications.

Preventive chemotherapy is the strategy of choice to control schistosomiasis, soil-transmitted helminthiases, lymphatic filariasis, onchocerciasis and food-borne trematodiases yet as emphasized in the following sections of this review, limited tools are available to treat these infections. In addition, for many of the available drugs, resistance is a threat since it has already developed in veterinary medicine and many of the drugs have an imperfect activity profile. Yet clear targets have been set to eliminate and control several of these diseases (http://www.unitingtocombatntds.org/downloads/press/london_declaration_on_ntds.pdf). Hence research and development (R&D) to find the next generation of anthelmintics is indispensable. However, a recent systematic assessment of databases of drug regulatory authorities and the World Health Organization (WHO) as well as clinical trial registries revealed a dry drug pipeline for NTDs, supported by the fact that no new chemical entity had been approved for these diseases in the past decade (Pedrique et al., 2013).

Drug repurposing (also termed re-profiling, re-tasking, therapeutic switching or drug repositioning) is the process of developing new indications for existing, failed or abandoned drugs or advanced clinical candidates (Sekhon, 2013). Drug repurposing is a useful strategy to accelerate the drug development process due to lower costs, reduced risk and decreased time to market due to availability of preclinical data (Padhy and Gupta, 2011). This enables not only pharmaceutical companies but also public-sector researchers to engage in drug discovery and development efforts (O'Connor and Roth, 2005), and hence might result in treatment options for diseases almost exclusively addressed by public sector researchers, such as the neglected tropical diseases. Over the past years, a variety of drug-repurposing initiatives have been launched with particular attention to neglected tropical and rare diseases (Allarakhia, 2013), hence it is likely that these efforts will bear fruit in the next years.

The aim of the present article is to highlight the status of drug repurposing for neglected helminth diseases. The focus is on the state-of-the-art treatments and how drug repurposing has been supplying the drug development pipeline for schistosomiasis, infections with major food-borne trematodes, *Fasciola* spp., *Opisthorchis* spp. and *Clonorchis sinensis*, soil-transmitted helminthiasis, *Strongyloides stercoralis*, the major human filariasis, lymphatic filariasis and onchocerciasis, taeniasis, neurocysticercosis and echinococcosis.

Our review complements a recent article by Andrews and colleagues which summarized antiprotozoal drug repurposing for major parasitic protozoal diseases including malaria, trypanosomiasis, and leishmaniasis (Andrews et al., 2014).

2. Schistosomiasis and food-borne trematodiases

2.1. Current treatment

Since its discovery in the 1970s, praziquantel has replaced many other drugs as the sole treatment for a range of helmintic infections. Praziquantel is effective against all three major species of *Schistosoma* (*S. mansoni*, *S. haematobium* and *S. japonicum*), and is the standard treatment against *C. sinensis*, *Opisthorchis viverrini* and *Opisthorchis felineus*, and intestinal flukes (Keiser and Utzinger, 2004; Utzinger and Keiser, 2004). It is administered orally, is safe, and highly effective.

As mentioned above, preventive chemotherapy is the strategy of choice to control schistosomiasis (WHO, 2006). This program is expected to expand ten-fold to include the treatment of 235 million people by 2018 (Knopp et al., 2013) which, on the one hand may significantly drive down morbidity and transmission but, on the other hand, would exacerbate drug pressure, likely resulting in resistance to praziquantel (Caffrey, 2007). Furthermore, praziquantel still has deficiencies: it is inactive against the juvenile stage of *Schistosoma* spp. and its (S)-enantiomer is inactive, a problem because at the moment, it is not separated from the (R)-enantiomer in production and hence the tablets are large and bitter (Stothard et al., 2013). Therefore, there is great motivation to seek alternative medications.

In the case of fascioliasis, triclabendazole is the treatment of choice (Keiser et al., 2005). Triclabendazole is safe and effective against both the human and veterinary forms of the disease. However, there are two major setbacks: in veterinary medicine, triclabendazole resistance has already been documented (Brennan et al., 2007). Additionally, triclabendazole is not registered for use in many nations, and is therefore not always available for the treatment of human fascioliasis (Keiser et al., 2005).

2.2. Repurposed drugs

2.2.1. Antimalarials and their derivatives

The largest anthelmintic drug repurposing success story by far has been the application of antimalarials against a wide variety of trematode infections, as well as other broader applications.

Investigations of the use of antimalarials against *Schistosoma* spp. and the liver flukes are based on the rationale that these flukes have the same blood-feeding characteristic as *Plasmodium* spp., and therefore share heme degradation mechanisms (Toh et al., 2010). If antimalarials target this pathway, they may also be effective against blood-digesting flukes. However, antimalarials have shown activity also against the non-blood feeding intestinal flukes (Ingram et al., 2012b), not only indicating their broad-spectrum activity, but also hinting at other mechanisms of action. As emphasized earlier, the use of antimalarials in de-worming programs should be eyed with caution, as this could accelerate resistance to these drugs. Nevertheless, since malaria and schistosome infections largely overlap geographically, the wide use of antimalarials might be beneficial in co-infected patients (Keiser and Utzinger, 2012).

2.2.1.1. Artemisinins. *Artemisia annua* (*quinghao*) has been used for thousands of years in Chinese medicine for a wide range of ailments, yet its antimalarial properties did not become known to the wider world until the 1970s, despite its prevalence as a common herb (Tu, 2011). Artemisinin, the plant's active ingredient, is a sesquiterpene lactone, with a characteristic peroxide bridge that is widely believed to be the active pharmacophore. Though potent, its short half-life, poor bioavailability and the reliance on plant cultivation spurred a search for semi-synthetic and completely synthetic alternatives (Ho et al., 2014). The most widely used artemisinin-derivatives are the first-generation semi-synthetics artesunate and artemether. Artemisinin-based therapies have shown great efficacy against *Schistosoma* spp., *Fasciola* spp., *Opisthorchis* spp. and *C. sinensis*, as summarized in previous reviews (Keiser and Utzinger, 2007b, 2012; Utzinger et al., 2007). Briefly, artemether, artesunate and dihydroartemisinin (the active metabolite of all artemisinin compounds) share common antischistosomal therapeutic characteristics. *In vivo* studies have demonstrated that these artemisinins are highly effective against juvenile infections and only moderately effective against adult infections (Keiser and Utzinger, 2012; Li et al., 2014). This observation suggests that these drugs particularly show clinical benefit when used as prophylactic treatments. Indeed, as calculated by a recent meta-analysis by Liu and colleagues, administration of multiple low doses of artemether or artesunate over a 1–2 week period achieved a protection rate of 65–97% against schistosomiasis japonicum (Liu et al., 2011). In addition, a decreased risk was observed using artemether for the prevention of *S. mansoni* and *S. haematobium* infections (Utzinger et al. 2000; N'Goran et al. 2003). Contradictory findings were obtained when these agents were used in the treatment of chronic infections. While some studies reported high efficacy, low to moderate cure rates (CRs) were observed in other trials (Keiser and Utzinger, 2007a). However, overall the therapeutic effect of artesunate, artemether or artemisinin based combination therapy (ACTs) against schistosomiasis was inferior to praziquantel in clinical trials (Keiser and Utzinger, 2007a; Utzinger et al., 2010). Finally, the artemisinins often showed synergistic effects with praziquantel in clinical trials, as elucidated by two meta-analyses (Liu et al., 2011; Perez del Villar et al., 2012).

The artemisinins have also been thoroughly characterized against food-borne trematodes in *in vivo* studies. Artemether and artesunate were both found to be very effective against the liver flukes *Fasciola hepatica* and *C. sinensis*, as well as the intestinal fluke *Echinostoma caproni* in the rodent infection models, achieving complete worm clearance (Keiser et al., 2006a,c,d), though lower worm burden reductions (WBRs) were achieved in the *O. viverrini* hamster infection model (66% and 78% for artemether and artesunate, respectively, administered as a single oral dose of 400 mg/kg) (Keiser et al., 2006d). Artemether and artesunate administered to sheep naturally infected with *F. hepatica* also achieved significant WBRs (91.3% at a dose of 140 mg/kg intramuscular (i.m.) and 91.9% at a dose of 40 mg/kg i.m. respectively), though embryotoxicity and toxicity were of potential concern (Keiser et al., 2008a, 2010e).

Studies with the artemisinins have progressed to clinical trials in *Fasciola*-infected patients: in central Vietnam, patients subjected to a 10-day treatment course with artesunate, administered daily at a dose of 4 mg/kg, were less likely to report abdominal pain at hospital discharge than patients treated with a standard oral dose of 10 mg/kg triclabendazole. However, 3 months post-treatment, clinical and serological response rates were lower among artesunate recipients compared to triclabendazole-treated patients (Hien et al., 2008). This result mirrors an exploratory Phase 2 trial conducted in Egypt, where chronically infected patients treated with 6×80 mg and 3×200 mg artemether only achieved CRs of 35 and 6%, respectively (Keiser et al., 2011). Finally, low CR and egg reduction rate (ERR) of 4% and 32% were also observed after administration of artesunate (10 mg/kg in 3 split doses) to school-aged children infected with *O. viverrini* (Soukhathammavong et al., 2011).

2.2.1.2. Synthetic peroxides. The success of the semi-synthetic artemisinins along with their pharmacologic draw-backs motivated the creation of fully synthetic derivatives in antimalarial drug discovery, the most investigated of these being the synthetic ozonides. The antimalarial OZ439 is currently in Phase 2 clinical trials (Wells, 2013). Two synthetic trioxolanes in particular have been widely investigated as potential anthelmintics- OZ78 and OZ288- whose trematocidal activity has been reviewed by Keiser and Utzinger (2007b). The review highlights the major *in vivo* studies which reveal interesting properties of these two compounds. First, their activity is comparable to those of the artemisinins and they exhibit the same increased *in vivo* activity against juvenile *S. mansoni* as compared to adult worms in mice and in hamsters. Second, in *S. mansoni in vivo* models, the adult WBR is affected by the rodent model, achieving only moderate WBRs in the mouse but high WBRs in the hamster model. However follow-up studies indicated similarly significant activity of OZ78 against *S. japonicum* juvenile and adult infection in hamsters, mice and rabbits, and of OZ277 in hamsters (Xiao et al., 2011, 2012). Interestingly, the ozonide OZ418 was recently found to be active against both juvenile and adult worms in the mouse *S. mansoni* infection model, and the adult *S. haematobium* hamster infection model (Keiser et al., 2012a), as well as moderately active against 7 day-old and adult *S. japonicum*- infected mice (Xue et al. 2014)- a result which shows that further modifications of the aryl ozonides can yield promising compounds.

With regard to the food-borne trematodes, *in vivo* activity of OZ78 against the liver flukes *F. hepatica* and *C. sinensis* and the intestinal fluke *E. caproni* is very high but studies with *O. viverrini* showed no activity at all (Keiser and Utzinger, 2007c). Importantly, in follow-up studies, OZ78 was found to be effective against triclabendazole-resistant *F. hepatica* (100% WBR at oral dose of 100 mg/kg) (Keiser et al., 2007a). Oddly, the high activity of the OZs against *F. hepatica* could not be repeated in naturally-infected sheep, regardless of the administration route (Keiser et al., 2010b; Meister et al., 2013). This discrepancy could potentially be explained by pharmacokinetic differences observed in rat and sheep, as discussed by Meister and colleagues (Meister et al., 2013).

Where OZ78 failed to treat *F. hepatica* in sheep, MT04 succeeded. MT04 is another synthetic peroxide, identified in the search for more effective analogues, which was found to have a 92% WBR and a 99% ERR in naturally infected sheep (Zhao et al., 2010; Wang et al., 2011; Meister et al., 2013).

Table 1
Trematocidal *in vivo* drug candidates.

			Adult infection		Juvenile infection		
Parasite	Drug	Host animal	Dose (mg/kg)	WBR (%)	Dose (mg/kg)	WBR (%)	References
Schistosoma mansoni	Dihydroartemisinin	Mouse	3 × 200–400	60–70	3 × 200–400	89–90	Li et al. (2012)
	OZ78	Mouse	400	52	200	95	Xiao et al. (2007)
		Hamster	200	85	100	83	Xiao et al. (2007)
	OZ288	Mouse	400	0	200	82	Xiao et al. (2007)
		Hamster	200	72	100	84	Xiao et al. (2007)
	OZ418	Mouse	400	96	200	100	Keiser et al. (2012a)
	Tribendimidine	Mouse	400	0	n.d.	n.d.	Keiser et al. (2007b)
	Imatinib	Mouse	3 × 1000	0	n.d.	n.d.	Katz et al. (2013)
	Miltefosine	Mouse	5 × 20	95	5 × 20	76	Eissa et al. (2011a)
	Nilutamide	Mouse	400	85	50–400	5–36	Keiser et al. (2010d)
	BTP-iso	Mouse	300	55	n.d.	n.d.	El Bialy et al. (2013)
	Clorsulon	Mouse	1–3 × 5	88–98	n.d.	n.d.	Mossallam et al. (2007)
	Anisomycin	Mouse	100	0	n.d.	n.d.	Abdulla et al. (2009)
	Lasalocid sodium	Mouse	100	41–44	n.d.	n.d.	Abdulla et al. (2009)
	Diffractic acid	Mouse	10–40	0	n.d.	n.d.	Abdulla et al. (2009)
	Gamboic acid	Mouse	100	0	n.d.	n.d.	Abdulla et al. (2009)
	Niclosamide	Mouse	100	0	n.d.	n.d.	Abdulla et al. (2009)
	Rafoxanide	Mouse	50	50–56	n.d.	n.d.	Abdulla et al. (2009)
Schistosoma haematobium	OZ418	Hamster	400	86	n.d.	n.d.	Keiser et al. (2012a)
Schistosoma japonicum	Dihydroartemisinin	Mouse	300	61	300	65	Li et al. (2011)
	OZ78	Hamster	200	70–94	200	73–81	Xiao et al. (2011)
		Rabbit	15	423	n.d.	n.d.	Xiao et al. (2012)
		Mouse	200–600	67–80	400	75	Xiao et al. (2012)
Fasciola hepatica	OZ78	Rat	100	100	100	100	Keiser et al. (2006b)
		Sheep	50–100	0	n.d.	n.d.	Keiser et al. (2010b), Meister et al. (2013)
	MT04	Sheep	100	92	n.d.	n.d.	Meister et al. (2013)
	Tribendimidine	Rats	800	0	n.d.	n.d.	Keiser et al. (2007b)
Clonorchis sinensis	OZ78	Rat	300	99	300	79	Keiser and Utzinger (2007a)
	Tribendimidine	Rat	150	98	n.d.	n.d.	Keiser et al. (2007b)
Opisthorchis viverrini	OZ78	Hamster	600	77	n.d.	n.d.	Keiser and Utzinger (2007a)
	Tribendimidine	Hamster	400	63	n.d.	n.d.	Keiser et al. (2007b)

WBR indicates worm burden reduction in relation to untreated control animals. n.d. denotes a lack of data.

2.2.1.3. Mefloquine. Mefloquine is a 4-quinolinemethanol whose discovery as an antimalarial dates to around the same time as the artemisinins. Its antischistosomal activity was revealed in 2008 and was thoroughly covered in a review by Xiao et al. (2013). This review highlights some excellent antischistosomal properties of mefloquine. First, it is active against all three major *Schistosoma* spp. and against both the juvenile and adult stages, a characteristic that neither praziquantel nor the artemisinins possess. Second, it causes severe morphological damage to the fluke and acts independently of the host immune response. Third, initial results from clinical trials were promising; mefloquine- artesunate achieved an ERR of 95% against *S. haematobium* in school-aged children (Keiser et al., 2010c). In addition, pregnant women who used mefloquine as intermittent preventive treatment for the prevention of malaria showed significantly higher CRs and ERRs against *S. haematobium* than women treated with sulfadoxine-pyrimethamine (Basra et al., 2013). Moreover, mefloquine-related arylmethanols also show antischistosomal activity *in vivo* (Ingram et al., 2012a).

The effectiveness of mefloquine against food-borne trematodes was briefly reviewed by Keiser et al. (2010a). This review highlighted that mefloquine is not active against *F. hepatica* nor *C. sinensis*, but interestingly, mefloquine was active against juvenile and adult *O. viverini* in a hamster infection model, achieving a WBR of 89% and 96% respectively, following a single oral dose of 300 mg/kg (Keiser et al., 2009a). However, mefloquine failed to produce an effect against *O. viverini* in clinical trials (Soukhathammavong et al., 2011). In a later study, mefloquine yielded significant results against *C. sinensis* infection in a rat model (when given at multiple dosages) and *Paragonimus westermani* infection in a dog model, but the results were not better than a treatment with praziquantel (Xiao et al., 2010).

2.2.2. Tribendimidine

Also originating from China, tribendimidine is a Chinese anthelmintic drug which has a similar activity profile against the soil-transmitted helminths as albendazole (high activity against *Ascaris lumbricoides* and hookworms but only moderate activity against *Trichuris trichiura*) (Xiao et al., 2013). Besides its broad range of antinematodal activity, tribendimidine has demonstrated trematocidal activity *in vivo* against *C. sinensis* and *O. viverrini* (Keiser et al., 2010a; Xiao et al., 2013). A recent randomized open-label trial in Guangxi, PR China presented moderate CRs (44% following a single dose of 400 mg/kg and 58% following 400 mg/kg administered once daily for 3 days) and high ERR (98–99%), similar to praziquantel. Tribendimidine compared favorably to praziquantel with regards to appearance of adverse events (Qian et al., 2013). Similarly, tribendimidine cured 19 of 24 patients infected with *O. viverrini* and achieved an ERR of 99% (Soukhathammavong et al., 2011). Further studies with tribendimidine are currently ongoing (e.g. dose-finding, pharmacokinetic studies) in *O. viverrini*-infected patients in Laos with the ultimate goal of developing an alternative opisthorchicidal drug.

To offset eventual resistance to praziquantel, using tribendimidine in combination with praziquantel is an attractive option. However, a recent study showed that praziquantel-tribendimidine administered to *O. viverrini*-infected hamsters, though achieving synergistic effects *in vitro*, had antagonistic effects in the hamster murine model (Keiser et al., 2013a). Further studies are required to shed light on this phenomenon. In contrast, in the *C. sinensis*

rat model, tribendimidine (12.5–50 mg/kg) showed synergistic interactions with 150 mg/kg praziquantel (Keiser et al., 2009b).

2.2.3. Other compounds

The most recent *in vivo* antitrematodal candidates come from a range of sources and fields, including cancer research, though expanding veterinary drug applications continues to be popular. The discoveries are described below and summarized in Table 1.

2.2.3.1. S. mansoni. A (well-funded) cancer drug pipeline provides a cornucopia of compounds. Dissous and Grevelding (2011) recently explored the potential of repurposing cancer drugs, specifically protein kinase inhibitors, towards schistosomiasis. The principal rationale was the identification of select protein kinases as being essential to schistosome development and the subsequent identification of certain cancer drugs as inhibitors of these kinases. However, most of the drugs discussed were only inhibitors of egg development and had little effect on the adult worms themselves. The one exception was imatinib (Gleevec), a successful anti-leukemia agent, which was shown to be lethal to adult worms *in vitro* at high concentrations (Beckman and Grevelding, 2010). However, imatinib was ineffective in an *S. mansoni* infection model (Table 1) (Katz et al., 2013) which is not surprising, as the drug is highly bound to alpha-1-acid glycoprotein (Soo et al. 2010).

Nonetheless, two anticancer agents have shown promising *in vivo* activity. Miltefosine, an alkylphospholipid, was initially developed to combat cutaneous metastasis of mammary carcinomas (van Blitterswijk and Verheij, 2013). As discussed in a complementary review by Andrews et al. (2014), it has also recently been licensed to treat leishmaniasis- a protozoan that also has cutaneous manifestations, though this drug treats both the visceral and cutaneous forms (Dorlo et al., 2012). Recently, it has shown *in vivo* activity in the *S. mansoni* mouse model at various stages of infection. Administered at 20 mg/kg for five consecutive days, commencing either on the day of infection (schistosomula stage), 21 days p.i. or 42 days p.i., miltefosine showed WBRs of 91%, 76% and 95%, respectively (Eissa et al., 2011a). A recent study by Eissa and colleagues also demonstrated its ovicidal, larvicidal and molluscicidal activity and its *in vitro* activity against *S. haematobium* adult worms (Eissa et al., 2011b). Interestingly, our own studies have shown that miltefosine was only moderately active against newly transformed schistosomula (NTS) of *S. mansoni* (unpublished findings).

The antiandrogen, nilutamide, blocks the binding of testosterone to the androgen receptor and was initially marketed for the treatment of metastatic prostate cancer (Akaza, 2011). Recently, we have tested it in the *S. mansoni* mouse model since related hydantoin derivatives studied at Hoffmann-La Roche had intriguing antischistosomal properties (Link and Stohler, 1984) – a single 400 mg/kg oral dose achieved a WBR of 85% and an even higher WBR was observed when given in combination with praziquantel (Keiser et al., 2010d). However, nilutamide did display a stage specific effect – it was only moderately active against the juvenile stage (Keiser et al., 2010d).

The advantages and disadvantages of using cancer drugs in the treatment of helmintic diseases should be carefully weighed. On the one hand, there is a great deal of effort to minimize toxic effects of cancer drugs due to their long treatment course. If a cancer drug is deemed safe when administered over a long period, there is a good chance it is also safe as an anthelmintic, where treatment is annual or twice annual (if part of regular preventive chemotherapy programs) but short (i.e. single dose). However, due to the severity and life threatening state of many cancers, the benefit of taking the drugs may outweigh potential severe adverse events. Thus, just because a drug is approved for cancer treatment, does not mean it is without significant adverse events. Yet a drug used in preventive chemotherapy programs must have an excellent tolerability profile.

Extending the application of veterinary anthelmintics continues to be a source of human anthelmintic candidates. Abdulla et al. (2009) showed that rafoxanide, a salicylanilide derivative and a veterinary anthelmintic, caused a 50–56% WBR in mice at a single oral dose of 50 mg/kg. This compound was identified from a screen of a commercially available FDA-approved library. This same screen also identified anisomycin, lasalocid sodium, diffractic acid, gamboic acid and niclosamide as hits for *in vivo* testing in the *S. mansoni* mouse model. Unfortunately, these drugs failed to reduce worm burden *in vivo,* the exception being lasalocid sodium which caused a WBR of 41–44% when administered at 100 mg/kg orally. Rafoxanide was not originally in the library, but due to niclosamide's excellent *in vitro* profile (but poor *in vivo* results), rafoxanide was tested as well, as it is structurally related to niclosamide. Clorsulon (a veterinary flukicidal drug) caused a WBR in *S. mansoni*-infected mice of 88%, 96% and 98% when treated with either a single, double or triple dose of 5 mg/kg one week apart starting from the 4th week postinfection (Mossallam et al., 2007). Yet in our own studies only moderate activity against NTS were observed *in vitro* when the NTS were incubated with 10 μM clorsulon for 72 h (unpublished observations).

Another re-purposing strategy is to increase the anthelmintic spectrum of activity through slight modification of the molecule. For example, BTP-Iso, a novel benzimidazole (in the same family as triclabendazole) was recently investigated as an antischistosomal. At a dose of 300 mg/kg given to *S. mansoni*-infected mice, BTP-Iso showed statistically significant higher reductions ($p < 0.01$) in female (77%), male (35%), and total worms (55%) in comparison with the control group (El Bialy et al., 2013).

2.2.3.2. F. hepatica. Two fasciocidal drugs were moved directly into clinical testing, without previous publications of *in vivo* studies. In Iran, 46 patients who were positive for *Fasciola* 3 months after triclabendazole treatment were given 1.5 g/day metronidazole orally for three weeks. Two months after end of therapy, stool exams became negative in 35 patients (81%), of which 31 patients (72%) presented both negative serology and stool exams. At 12 months, 28 patients were examined and all were negative (Mansour-Ghanaei et al., 2003).

Nitazoxanide, a thiazolide derivative and a pyruvate ferredoxin oxireductase inhibitor, has a broad spectrum of activity. The US Food and Drug Administration (FDA) approved nitazoxanide in 2002 for the treatment of diarrhea caused by *Cryptosporidium* species and *Giardia intestinalis* in pediatric patients 1–11 years of age, and in 2004 for its use in adults (Hemphill et al., 2006). Two clinical trials elucidated nitazoxanide's fasciocidal effects. In northern Peru, a double-blind placebo-controlled trial showed moderate effects in children and adults: a 7-day course of nitazoxanide resulted in CRs of 60% in adults and 40% in children (Favennec et al., 2003). In the Atlixco municipality in Mexico, a study carried out in 50 Mexican schoolchildren showed nitazoxanide to be effective against light *F. hepatica* infections. Children diagnosed with fascioliasis were administered nitazoxanide at 7.5 mg/kg body weight, every 12 hours over seven days. The efficacy against fascioliasis was 94% and 100% after first and second treatment courses, respectively. Its efficacy was also very high against protozoan and intestinal helminths (Zumaquero-Rios et al., 2013). However, this second study did not have a control group, and therefore could not be compared to a placebo or treatment with triclabendazole. Given these somewhat contradictory findings, larger randomized control trials should be conducted to elucidate the role of nitazoxanide in the treatment of fascioliasis.

Myrrh has been marketed as an antischistosomal, though its actual effect is controversial (Abdul-Ghani et al., 2009; Yakoot,

2010). Despite a 2004 field trial in Egypt, showing a CR of 88% and 94% CR, 2 and 3 months after treatment (Abo-Madyan et al., 2004), the overall consensus based on bench and field publications is that it is ineffective as a fasciocidal agent (Botros et al., 2009; Keiser et al., 2010a).

In the veterinary field, the benzimidazoles are often used as broad-spectrum anthelmintics, as discussed further in the soil-transmitted helminths section below. In livestock, the use of oxfendazole has previously been restricted to the treatment of roundworm, strongyloides and pinworm infection. However, very recently, it was demonstrated that it has potent anti-flukicidal activity: 100% WBR was achieved after a single oral dose of 30 mg/kg was given to *F. hepatica* infected pigs (Ortiz et al. 2014).

3. Soil-transmitted helminthiasis and strongyloides

3.1. Current treatment

The two benzimidazoles, albendazole and mebendazole, as well as pyrantel pamoate and levamisole are the four available treatments against soil-transmitted helminths, marketed between 1966 (pyrantel pamoate) and 1980 (albendazole) (Keiser and Utzinger, 2010; WHO, 2013). These drugs are widely used (in 2010, 328 million children were treated with albendazole or mebendazole (Anonymous, 2012)) since, as mentioned, the current strategy to control morbidity due to the most common soil-transmitted helminths (*A. lumbricoides*, *T. trichiura* and the hookworm species *Ancylostoma duodenale* and *Necator americanus*) is by regular treatment of at risk populations (WHO, 2006, 2011). The limitations of these drugs are widely known. Briefly, using a single dose regimen they all are very efficacious against *A. lumbricoides*, yet for the treatment of hookworm infections only albendazole produces satisfying CRs, while all drugs achieve poor CRs against infections with *T. trichiura* (Keiser and Utzinger, 2008). As no new anthelmintic drugs are on the horizon, repurposing of existing drugs is an essential strategy to improve treatment of soil-transmitted helminths, particularly *T. trichiura* infections (Keiser and Utzinger, 2008; Olliaro et al., 2011).

The current drug of choice against *S. stercoralis* infections is ivermectin, which is widely used in mass drug administration programs to combat lymphatic filariasis (Knopp et al., 2012a). A single dose of 200 μg/kg results in a CR of 88% against *S. stercoralis* (Keiser and Utzinger, 2010). The drug has the disadvantages that it is not licensed for treating *S. stercoralis* infections in several countries (e.g. Switzerland, Germany, Great Britain), that the ideal dosage schedule of ivermectin has yet to be evaluated, and that it can cause harmful and dangerous treatment effects in individuals co-infected with *Loa loa* which is an insect-borne filarial infection (Bisoffi et al., 2013; Greaves et al., 2013). People not tolerating ivermectin can alternatively use albendazole, which is inferior compared to ivermectin regarding ERRs and CRs; however, it still achieves satisfactory efficacy (Keiser and Utzinger, 2010; Knopp et al., 2012a). In addition, mebendazole achieves CRs and ERRs of 67–98% against *S. stercoralis* when given in multiple doses (Musgrave et al., 1979; Shikiya et al., 1990, 1991; Zaha et al., 2000). Of note, even though ivermectin is not listed as an essential drug against soil-transmitted helminths (WHO, 2013), several studies have shown that by combining ivermectin with the standard drug albendazole or mebendazole, the efficacy against soil-transmitted helminths (especially against *T. trichiura*) can be improved significantly (a summary of trials is presented in Keiser et al. (2012b)).

3.2. Repurposed drugs

3.2.1. Drugs evaluated in clinical testing

3.2.1.1. Nitazoxanide. Nitazoxanide, mentioned above for its protozoan and fasciocidal properties, showed (in manufacturer-financed trials) very high CRs against *A. lumbricoides*, *T. trichiura*, *S. stercoralis* and even against *A. duodenale* when the drug was given in multiple doses (Romero Cabello et al., 1997; Abaza et al., 1998; Juan et al., 2002; Diaz et al., 2003). The drug also demonstrated superior activity than the standard drugs in *in vitro* screening against *Trichuris muris* (Tritten et al., 2012). However, a recent clinical trial using a single dose of 1000 mg nitazoxanide could not confirm the initial results obtained in earlier trials and in the laboratory. Nitazoxanide achieved low CRs and ERRs (7% and 13%, respectively) against *T. trichiura* in school-aged children on Pemba, Tanzania. Additionally the drug was slightly less well tolerated compared to standard treatment and hence nitazoxanide was not recommended as an alternative treatment against soil-transmitted helminthiasis (Speich et al., 2012). Of note, within the same trial, the efficacy of a single dose nitazoxanide (1000 mg) against intestinal protozoa was also only moderate (Speich et al., 2013).

3.2.1.2. Oxantel pamoate. Oxantel pamoate, a veterinary drug which was introduced on the market in 1974, revealed high efficacy against *T. trichiura* in a number of exploratory trials (Garcia, 1976; Lee et al., 1976; Lee and Lim, 1978). The drug was only revisited recently, more than three decades later. Laboratory studies demonstrated a significantly higher activity of oxantel pamoate compared to the benzimidazoles, levamisole or pyrantel pamoate against *T. muris in vitro* and *in vivo* (Keiser et al., 2013b). A randomized controlled double blind trial recently confirmed the high efficacy of oxantel pamoate (20 mg/kg) against *T. trichiura* (26% CR and 93% ERR). Hence oxantel pamoate-albendazole, due to its broad spectrum of activity could be useful in the control of soil-transmitted helminthiasis (Speich et al., 2014). Further studies have been planned with the ultimate goal of elucidating the potential of adding oxantel pamoate to the current drug armamentarium.

3.2.1.3. Tribendimidine. A large phase 2 trial in Côte d'Ivoire confirmed the excellent activity of tribendimidine against hookworm and *A. lumbricoides* (N'Goran et al. under review). Following promising results with tribendimidine against *Strongyloides ratti* in the rat model (Keiser et al., 2008b) an exploratory trial in China documented a CR of 55% in patients infected with *S. stercoralis* (Steinmann et al., 2008).

3.2.1.4. The benzimidazoles. The benzimidazoles are a large family, widely used in veterinary medicine, and not only include albendazole and mebendazole (and the fasciocidal drug triclabendazole mentioned earlier) but also flubendazole, fenbendazole, oxfendazole, thiabendazole and oxibendazole (Olliaro et al., 2011). In addition, oxfendazole and cambendazole are promising broad spectrum benzimidazoles used in veterinary medicine, which have not yet been tested in humans. The benzimidazoles have a broad spectrum of activity including whipworms, roundworms and hookworms. For example, multiple doses of thiabendazole have similarly high efficacy against *S. stercoralis* as compared to ivermectin, however the drug was less tolerated (Gann et al., 1994; Zaha et al., 2000; Bisoffi et al., 2011). Clinical trials conducted with flubendazole, fenbendazole, oxibendazole and thiabendazole against soil-transmitted helminths and *S. stercoralis* are summarized in Table 2.

3.2.2. Compounds in early clinical testing and potential veterinary drugs

An excellent summary of potential drug development candidates for human soil-transmitted helminthiasis has recently been provided by Olliaro and colleagues (Olliaro et al., 2011).

Four promising compound classes are worth highlighting. First, emodepside is a cyclic depsipeptide and a broad-spectrum veterinary anthelmintic used for companion animal gastrointestinal

Table 2
Drugs tested in clinical trials against soil-transmitted helminths (See below-mentioned references for further information).

Drug tested	Number of patients	Dose	Cure rate	Egg reduction rate	Reference
Oxantel pamoate	*T. trichiura*: 12-122	10-25 mg/kg	*T. trichiura*: 57-93%	*T. trichiura*: 90-96%	(Lee et al., 1976)
	A. lumbricoides: 53 *T. trichiura*: 10-26	10-20 mg/kg	*A. lumbricoides*: 0% *T. trichiura*: 77-100%		(Garcia, 1976)
	79 *A. lumbricoides* 114 *T. trichiura* 113 Hookworm	20 mg/kg	*A. lumbricoides*: 10% *T. trichiura*: 26% Hookworm: 11%	*A. lumbricoides*: 28% *T. trichiura*: 93% Hookworm: 39%	(Speich et al., 2014)
Nitazoxanide	*A. lumbricoides*: 33-144 *T. trichiura*: 9-86	7.5 mg/kg (500 mg to adults, 200 mg to children under 12 years) every 12 hours for 3 consecutive days	*A. lumbricoides*: 48-100% *T. trichiura*: 56-78%	*A. lumbricoides*: 99.7-100% *T. trichiura*: 99.5-99.6%	(Romero Cabello et al., 1997)
	A. lumbricoides: 155 *T. trichiura*: 29 Hookworm: 46 *S. stercoralis*: 36	500 mg to adults, 200 mg to children 4 to 11 years, and children 1 to 3 years 100 mg every 12 hours for 3 consecutive days	*A. lumbricoides*: 95% *T. trichiura*: 86% Hookworm: 96% *S. stercoralis*: 94%		(Abaza et al., 1998)
	A. lumbricoides: 35 *T. trichiura*: 18 *S. stercoralis*: 6	200 mg to children 4 to 11 years, and 100 mg to children 1 to 3 years every 12 hours for 3 consecutive days	*A. lumbricoides*: 89% *T. trichiura*: 89% *S. stercoralis*: 83%	*A. lumbricoides*: 99.9% *T. trichiura*: 99.8%	(Juan et al., 2002)
	A. lumbricoides: 8 *T. trichiura*: 136 Hookworm: 12	1000 mg single dose	*A. lumbricoides*: 63% *T. trichiura*: 7% Hookworm: 67%	*T. trichiura*: 13%	(Speich et al., 2012)
Oxibendazole	*A. lumbricoides*: 196 *T. trichiura*: 178 Hookworm: 340	15 mg/kg/day for 3 days	*A. lumbricoides*: 93-98% *T. trichiura*: 67-71% Hookworm: 70-81%	Hookworm: 98-99%	(Huang et al., 1990)
Fenbendazole	*A. lumbricoides*: 2-7 *T. trichiura*: 6-17 Hookworm: 5-31	1 g and 1.5 g as single doses and 2 x 500 mg over 24 hours	*A. lumbricoides*: 60-100% *T. trichiura*: 65-100% Hookworm: 8-26%		(Bruch and Haas, 1976)
	A. lumbricoides: 2 *T. trichiura*: 14 Hookworm: 18 *S. stercoralis*: 14	6 x 600 mg each 12 hours	*A. lumbricoides*: 100% *T. trichiura*: 93% Hookworm: 89% *S. stercoralis*: 29%		(Sanchez-Carrillo and Beltran-Hernandez, 1977)
	A. lumbricoides: 31 *T. trichiura*: 28 Hookworm: 18	30-50 mg/kg	*A. lumbricoides*: 84% *T. trichiura*: 29% Hookworm: 83%	*A. lumbricoides*: 97% *T. trichiura*: 38% Hookworm: 82%	(Rim et al., 1981)
Flubendazole	*A. lumbricoides*: 3-5 *T. trichiura*: 4-16 Hookworm: 27-60	2 x 300 mg (spaced by 12 or 24 hours)	*A. lumbricoides*: 100% *T. trichiura*: 38-100% Hookworm: 30-82%	*A. lumbricoides*: 100% *T. trichiura*: 43-100% Hookworm: 88-96%	(Bunnag et al., 1980)
	T. trichiura : 19	100 mg twice a day for 3 days	*T. trichiura*: 89%	*T. trichiura* : >99%	(Yangco et al., 1981)
	A. lumbricoides: 33-47 *T. trichiura*: 32-52	200-600 mg, 300 x 2 mg	*A. lumbricoides*: 90-97% *T. trichiura*: 17-65%	*A. lumbricoides*: 98.7-99.6% *T. trichiura*: 91-95%	(Kan, 1983)
	A. lumbricoides: 43-47	500 mg or 200 mg	*A. lumbricoides*: 86-89%	*A. lumbricoides*: 97-98%	(de Silva et
	T. trichiura: 43-47		*T. trichiura*: 19-26%	*T. trichiura*: 42-54%	al., 1984)
Thiabendazole	*S. stercoralis*: 103	25 mg/kg twice a day for 3 days	*S. stercoralis*: 79%		(A.A. et al., 2003)
	S. stercoralis: 92	25 mg/kg twice a day for 2 days	*S. stercoralis*: 52%		(Bisoffi et al., 2011)
	S. stercoralis: 19	50 mg/kg/day twice a day for 3 days	*S. stercoralis*: 89%		(Gann et al., 1994)

nematode infections (Harder et al., 2003; Geary and Mackenzie, 2011). It showed high activity against *Trichuris* spp., *Ancylostoma* spp. and other nematodes in *in vitro* and *in vivo* studies (Harder and von Samson-Himmelstjerna, 2002; Altreuther et al., 2009). Moreover, the closely related PF1022A was potent in clearing *T. muris* infections in mice at various stages of infection (Kulke et al. 2014). *In vivo* studies on *Haemonchus contortus* have shown that it has a different mode of action than the benzimidazoles and ivermectin (von Samson-Himmelstjerna et al., 2005) hence the drug will likely be active against parasites resistant to the benzimidazoles and ivermectin.

Second, doramectin which belongs to the avermectins, showed high efficacy against *S. ransomi*, *S. papillosus*, *T. suis* and *A. suum* in pigs (Stewart et al., 1996; Yawzinski et al., 1997) as well as against *Trichuris* spp. in cattle (Jones et al., 1993; Saeki et al., 1995). Doramectin showed even more favorable results against nematodes compared to ivermectin, which could be explained by its lower clearance and higher bioavailability (Lumaret et al., 2012). The closely related milbemycin family is also a potent drug class. Milbemycin oxime has proven to be efficacious against *Ascaris* spp., hookworm and *Trichuris* spp. in cats and dogs (Blagburn et al., 1992; Catton and Van Schalkwyk, 2003). On the other hand only low ERRs were found against *T. trichiura* in baboons (Reichard et al., 2007).

Third, moxidectin is another commercially available broad-spectrum antiparasitic from the veterinary field (Reinemeyer and Cleale, 2002). It is a semisynthetic methoxime derivative of naturally occurring nemadectin with a novel mode of action (Awasthi et al., 2013). Moxidectin showed high efficacy in several *in vivo* studies (i.e. in cattle, swine, sheep) against *Ascaris* spp., *Trichuris* spp. and *Strongyloides* spp. (Bauer and Conraths, 1994; Coles et al., 1994; Stewart et al., 1999; Reinemeyer and Cleale, 2002; Ranjan and DeLay, 2004; Lyons et al., 2006).

Finally, from a completely different medical arena, cyclosporine A is an immunosuppressive agent which is commonly used for organ transplantation (Cohen et al., 1984). Its antischistosomal properties were first described in 1981 (Bueding et al., 1981) followed by studies against *S. stercoralis* in dogs and *S. ratti* in rats (Armson et al., 1995). Treatment with cyclosporine A seems to be of benefit in cases of opportunistic, possibly life threatening infections of *S. stercoralis* activated by immunosuppression (Schad, 1986).

4. Filariasis

4.1. Current treatment

Though filariasis is a collection of diseases, the three major control programs target lymphatic filariasis (Global Program to Eliminate Lymphatic Filariasis) or onchocerciasis (African Program for Onchocerciasis Control and the Onchocerciasis Elimination

Program for the Americas), and a major cornerstone of all three programs is mass drug administration. Regardless of the disease, the recommended treatments are limited: ivermectin, albendazole and diethylcarbamazine (DEC), ivermectin being the most widely recommended drug. The use and status of these drugs, including their limitations, have recently been reviewed by Katiyar and Singh (2011). Briefly, resistance to ivermectin has already been documented and its administration to onchocerciasis patients co-infected with loaiasis results in severe adverse events (Kamgno et al., 2007). Albendazole's efficacy is heavily debated and DEC is contraindicated in patients with onchocerciasis (Katiyar and Singh, 2011). Additionally, the treatment regimens required for these drugs in order to fully stop transmission are long: according to current control guidelines, ivermectin or DEC-albendazole need to be administered once a year for 5 years to interrupt LF transmission (Anonymous, 2009, 2014). The long treatment schedule is partly because all three drugs predominantly act on microfilaria only (the larvae shed by the adult worms), with DEC showing some adult stage activity (Dreyer et al., 2006). This latter point is problematic, as the adult stage still survives in the host, ready to shed more microfilaria once the drugs are absent from the host, continuing to cause pathology in onchocerciasis patients and also continuing the transmission cycle. Thus, new drug candidates should necessarily target adult worms as well. Additionally, as all filariasis-causing nematodes (except *L. loa*) carry with them the endosymbiotic *Wolbachia* bacteria necessary for the parasite's development, efforts have been made to target these bacteria.

4.2. Drugs targeting Wolbachia

Amongst the new antifilarial drugs, doxycycline is the most studied. It is a broad-spectrum antibacterial and antiprotozoal whose effects against *Wolbachia* are considered a breakthrough in antifilarial treatment (Katiyar and Singh, 2011). In onchocerciasis patients, a treatment regimen of 100 mg of doxycycline per day for 6 weeks slowly eliminated *Wolbachia* and resulted in long-term embryogenesis block of the adult worms (Hoerauf et al., 2003). The death of *Wolbachia* also leads to macrofilaricidal effects, as adults worms extracted from LF patients treated with 200 mg of doxycycline per day for 4 weeks were found to be either sterile or dead (Debrah et al., 2007). Findings by Taylor and colleagues also showed macrofilaricidal effects in LF patients, though the same level of potency could not be observed in onchocerciasis patients (Taylor et al., 2005; Hoerauf et al., 2008b). In addition, doxycycline is potentially microfilaricidal as well, as shown in LF patients treated with 100–200 mg per day for 6 weeks (Supali et al., 2008). Doxycycline, given prior to antifilarial treatment, appears to be more effective in suppressing microfilaremia in bancroftian filariasis over the long term than the standard treatments alone, while also resulting in fewer severe adverse events (Turner et al., 2006). LF symptoms could also be reduced by doxycycline, regardless of active filarial infection as demonstrated in a trial in Ghana (Mand et al., 2012). This symptomatic alleviation also extends to LF patients who presented with hydrocele (Debrah et al., 2009).

The effects of doxycycline administered in combination with the standard drugs have also been characterized. For example, a combination of doxycycline and albendazole was far more effective at suppressing circulating microfilaria than doxycycline or albendazole alone (nearly 100% suppression vs. 69% and 89%, respectively when checked at day 365 post-treatment) and even succeeded in completely clearing 42% of patients of microfilaremia (Gayen et al., 2013). Different trials also assessed doxycycline/ivermectin and found that the combination was more effective than ivermectin or doxycycline alone (Masud et al., 2009; Turner et al., 2010). Similarly, a 21-day course of doxycycline at 200 mg administered orally to LF patients in Orissa, India, followed by a single 6 mg/kg dose of DEC was effective at completely clearing microfiladermia. Interestingly, the co-administration of doxycycline followed by DEC was also effective at clearing adult worm nests, and less effective when the doxycycline treatment was shortened to 10 days (Mand et al., 2009).

Doxycycline was even found to be effective against *Mansonella perstans*, one of two agents that cause serous cavity filariasis. In a randomized open-label trial in Mali, 97% and 75% of *M. perstans* patients treated with 200 mg doxycycline for 6 weeks were found to be amicrofilaremic at 12 and 36 months post-treatment, respectively. This finding is very significant as the current standard treatments are not effective against *M. perstans* (Coulibaly et al., 2009).

Last but not least, given that *L. loa* is the only filarial nematode that does not possess *Wolbachia* endosymbionts, the use of *Wolbachia*-targeting antibiotics is a possible safe alternative for the treatment of this disease. Doxycycline was already shown to be safe in onchocerciasis patients co-infected with loaisis (Wanji et al., 2009; Turner et al., 2010), but its long treatment course leaves room for short-course therapy innovations.

Considering the importance of a potent anti-*Wolbachia* treatment, there is ongoing research to also elucidate the effects of other potent broad-spectrum antibiotics on *Wolbachia*. Rifampicin was found to be effective in reducing *Wolbachia* bacteria, as well as embryogenesis and microfilaria production in a small number of onchocerciasis patients, though not as efficiently as doxycycline (Specht et al., 2008). However a short-course therapy of 5 days rifampicin was documented to be completely ineffective (Richards et al., 2007). Meanwhile azithromycin was observed to be only marginally effective against *Wolbachia* and showed no effect on the worms in onchocerciasis patients in Ghana (Hoerauf et al., 2008a). In another study, oxytetracycline (the parent compound of doxycycline) had macrofilaricidal properties in cattle infected with *Onchocerca ochengi*, however this success has yet to be translated to human treatment (Nfon et al., 2007).

4.3. Drugs targeting the worms

As mentioned above, drugs effective against the filarial adult stage should be investigated with high priority. The potential of the benzimidazole flubendazole, a veterinary drug used to treat gastrointestinal nematode infection, as a pre-clinical macrofilaricide candidate for preventive treatment of onchocerciasis and lymphatic filariasis is currently being studied in a project lead by the Drugs for Neglected Diseases *initiative* (DND*i*). These investigations have been reviewed by Mackenzie and Geary (2011). In the late 1980s and early 1990s, flubendazole was shown to be macrofilaricidal against a variety of filariases-causing agents *in vivo* and even in a clinical trial for onchocerciasis (Dominguez-Vazquez et al., 1983; Van Kerckhoven and Kumar, 1988; Franz et al., 1990). Interestingly, it has no microfilaricidal effects (Van Kerckhoven and Kumar, 1988), which indicates that it could be safe for *L. loa* co-infected patients as well. The drug is, however, very poorly orally absorbed and hence the current focus of the project lead by DND*i* is to improve the drug's bioavailability. A new cyclodextrin formulation is currently being investigated with mixed results: while it achieved higher plasma concentrations when administered orally to *Echinococcus granulosus*-infected mice, no significant pharmacokinetic effects were observed when it was administered to sheep via the intraruminal nor the intraabomasal route (Ceballos et al., 2009, 2012).

Nonetheless, other drugs on the horizon continue to target microfilaria while also having some effects on the adult stage. Unsurprisingly, moxidectin has shown potent microfilaricidal effects and long term sterilization of females. Furthermore, early-stage clinical trials have shown that it is safe and well tolerated in humans in doses of 3–36 mg and has a longer half-life than

ivermectin (Cotreau et al., 2003; Awadzi et al. 2014). It is being evaluated in ongoing Phase 2 and 3 clinical trials via a partnership between APOC, TDR and Wyeth (Taylor et al., 2009; Babalola, 2011). Nonetheless, tolerability studies are needed to confirm that moxidectin is safe in patients co-infected with *L. loa* and whether the drug is efficacious against ivermectin-resistant filaria.

Other anthelmintics tested include the above mentioned cyclic depsipeptides, emodepside and PF1022A, and levamisole. Emodepside showed potent microfilaricidal effects and even some macrofilaricidal effects (but not against *Brugia malayi*) *in vivo* (Zahner et al., 2001), hence there is great interest in the potential of emodepside as a novel antifilarial (http://r4d.dfid.gov.uk/PDF/Outputs/DNDI/evolutions_of_dndi_portfolio.pdf). With regards to levamisole, though previous studies from the 1980s showed it had no significant treatment effect for LF or onchocerciasis patients (Awadzi et al., 1982; McMahon, 1981), the drug was revisited in a clinical trial in 2004 where levamisole was given alone (2.5 mg/kg) or co-administered with ivermectin or albendazole. Here as well, it proved to be ineffective, alone or in combination (Awadzi et al., 2004).

Nitazoxanide, mentioned earlier in this review, and its metabolite tizoxanide were tested against *B. malayi* worms *in vitro* and *in vivo*. The drugs were lethal to adult worms at 20 μg/ml and significantly decreased microfilaria release at 5 μg/ml. However, they were ineffective against *Wolbachia* and eventually were shown to be ineffective in clearing the worms *in vivo* (Rao et al., 2009).

Considering the success of antimalarials against trematodes, as well as the co-endemicity of malaria and many helmintic diseases, it is always tempting to test antimalarials on other worms as well. Recently, an open randomized control trial investigated the effects of the antimalarials quinine, chloroquine, amodiaquine and artesunate, based on previous *in vivo* successes or case studies, on patients infected with *L. loa*. However, none of the treatments were found to be effective (Kamgno et al., 2010).

5. Cestode infections

5.1. Current treatment

Niclosamide, originally developed as a molluscicide, was introduced in 1959 as the first synthetic drug against taeniasis, characterized by an excellent therapeutic index and high efficacy (WHO/FAO/OIE, 2005). It is a poorly water soluble halogenated salicylanilide with a low bioavailability, which is an advantage since a systemic action is not desired (Pearson and Hewlett, 1985; WHO/FAO/OIE, 2005). Approximately one decade later, in 1972, the taenicidal activity of praziquantel, an acylated isoquinoline-pyranzine, was discovered jointly by Bayer AG and E. Merck (Andrews et al., 1983). Both drugs are still the recommended first line treatments against intestinal cestodes including *Taenia solium*, *Taenia saginata*, *Diphyllobothrium* spp. and *Hymenolepis nana* (WHO/FAO/OIE, 2005). Praziquantel, which is well absorbed from the intestine, presents additional activity against *T. solium* cysticerci located in the host's tissues (i.e. central nervous system, subcutaneous tissue, and the eye). A single oral dose of praziquantel is highly effective against taeniasis; nevertheless multiple treatment courses over 2 weeks are recommended for uncomplicated cysticercosis. Albendazole, is also recommended for the treatment of (neuro)-cysticercosis and is generally more active than praziquantel (Sotelo et al., 1988, 1990; Takayanagui and Jardim, 1992; WHO/FAO/OIE, 2005). Regardless, therapy for neurocysticercosis needs to be individualized depending on the patient's state of disease. Anthelmintics, surgery, and symptomatic treatment with analgesics, corticosteroid drugs, and antiepileptic drugs, to relieve headache, perilesional inflammation and seizures, are the main pillars of the therapeutic approach (Carpio, 2002; Garcia et al., 2011).

Surgical resection of the entire parasitic lesion is indicated in all operable cases of cystic and alveolar echinococcosis. Puncture-aspiration-injection-re-aspiration (PAIR) treatment is applied in inoperable cases of cystic echinococcosis: cysts are punctured and exposed to protoscolicidal substances (i.e. ethanol 95%) for at least a quarter of an hour (WHO, 1996). Chemotherapy is key to preventing secondary echinococcosis and to reducing the risk of re-occurrence following surgery (Brunetti et al., 2010). Mebendazole and albendazole are both recommended for the treatment of echinococcosis. The albendazole dose regimen is more convenient because its phase-1 metabolite, albendazole sulfoxide, also exhibits metacestodicidal properties and thus the drug disposition is greater than for mebendazole (Ingold et al., 1999). Praziquantel itself possesses less pronounced activity against echinococcosis than albendazole. Combination treatment of praziquantel and albendazole seems sensible, because both drugs display a different mechanism of action and praziquantel increases the bioavailability of albendazole sulfoxide when the two are given together (Cobo et al., 1998; Kern, 2006; Garcia et al., 2011). Nonetheless, insufficient clinical data are available to provide treatment recommendations for this combination (Pawłowski, 2001; Bygott and Chiodini, 2009).

5.2. Repurposed drugs

5.2.1. Taeniasis and neurocysticercosis

The food and drug administration (FDA) approved nitazoxanide, mentioned several times earlier in this review, as an antiprotozoal agent against *Cryptosporidium* species and *Giardia intestinalis* in 2002 (Rossignol, 2009). Its chemical structure stems from the taenicide niclosamide and therefore, unsurprisingly, activity was reported against *T. saginata* and *H. nana* infections in the 1980s (Table 3) (Rossignol and Maisonneuve, 1984). Hence, nitazoxanide is not a genuine example of a repurposed drug for taeniasis; still its strong taenicidal activity makes it attractive for off-label use in cases where patients do not respond to praziquantel or niclosamide (Vermund et al., 1986; Lateef et al., 2008). Similarly, quinacrine (mepacrine), which is an ancient antimalarial agent and antigiardial drug, can be used to treat niclosamide-tolerant *T. saginata* infections (Gardner et al., 1996; Koul et al., 2000).

The recent promising results achieved with tribendimidine against *O. viverrini* and *C. sinensis* liver fluke infections (see above) inspired further exploration of its anthelmintic activity profile against cestodes. In an open-label randomized clinical trial, including 15 patients infected with *Taenia* spp., a single oral dose of 200 mg (5–14 year old children) or 400 mg ($\geqslant$15 years) tribendimidine resulted in a CR of 67%. Due to diagnostic challenges and the relatively small numbers of patient enrolled in the study, the authors pointed out that the observed cestocidal effect of tribendimidine should rather be recognized as an indication of possible activity rather than as a proof-of-concept (Steinmann et al., 2008). A distinct anticestodal potential of tribendimidine was demonstrated in mice infected with *Hymenolepis microstoma*, where a triple dose of 50 mg/kg tribendimidine, given over three consecutive days, achieved a WBR of more than 95% (Kulke et al., 2012). No cestocidal effect was observed however, when mice were treated with deacetylated amidantel. This result is somehow unexpected as deacetylated amidantel is supposed to be the major active metabolite of tribendimidine, hence further studies are required (Xiao et al., 2009; Yuan et al., 2010).

Paromomycin (Humatin®) is an aminoglycoside antibiotic with activity against gram-negative and various gram-positive bacteria. It is marketed to decrease bacterial load in the gut in hepatic coma, and for the treatment of amoebiasis and giardiasis. Recently, it has been licensed in India for leishmaniasis therapy (Davidson et al., 2009). In the 1960s the taenicidal activity of paromomycin was

discovered by chance in the course of amoebiasis treatments, where co-infected patients shed segments of *T. saginata* (Salem and el-Allaf, 1969). In a follow-up clinical study it was demonstrated that daily treatments for 1–3 days with 30–50 mg/kg paromomycin resulted in a success rate of 89–100% against *T. saginata*. In addition, an efficacy of approximately 90% was observed against *H. nana* following a 30 mg/kg single or double dose of paromomycin (Salem and el-Allaf, 1969).

Tamoxifen is a first generation selective estrogen receptor modulator (SERM), which acts as an antagonist on estrogen receptors in breast tissue, while possessing an agonistic effect in other tissues. It is used as an adjuvant for breast cancer and the palliative treatment of metastatic or locally advanced mamma carcinoma (den Hollander et al., 2013). It has been demonstrated that estradiol plays an essential role in regulating the asexual reproduction of *Taenia crassiceps* cysticerci in mice, possibly by interfering with the host's cellular immune response (Terrazas et al., 1994), and as a result, tamoxifen was tested against *T. crassiceps* cysticerci. Tamoxifen reduced the parasite load by 80% and 50% in female and male mice, respectively. In addition, loss of motility and reduced reproduction could be demonstrated *in vitro* (Vargas-Villavicencio et al., 2007). A follow-up study showed that tamoxifen decreased the intestinal establishment of *T. solium* in hamsters by approximately 70%. Moreover, tamoxifen induced morphological changes: the recovered tapeworms appeared like scolices without strobilar development and consequently showed an 80% reduction in length (Escobedo et al., 2013). Yet the taenicidal and cysticidal potential of tamoxifen has not been evaluated in humans and livestock.

Metrifonate is an organophosphorous compound applied as an insecticide and veterinary anthelmintic. In humans it has been, for example, for the treatment of schistosomiasis (Holmstedt et al., 1978). A case report published in 1981 about a man with a heavy cutaneous cysticercosis infection, described that two treatment courses of metrifonate at 10 mg/kg/day for six days were able to clear about 75% of the nodules and reduced the size of the remaining ones. Nevertheless, the observed adverse drug events caused by metrifonate's unspecific cholinesterase inhibition were so strong that atropine had to be given to relieve the symptoms (Tschen et al., 1981).

5.2.2. Echinococcosis

In vitro and *in vivo* studies indicate that *Echinococcus multilocularis* and *E. granulosus* can be included in the broad activity spectrum of nitazoxanide. *In vitro* treatment of *E. multilocularis* metacestodes with nitazoxanide lead to morphological and ultrastructure alterations and inhibited larval growth, while *E. granulosus* protoscoleces and metacestodes suffered deleterious effects as well (Stettler et al., 2003; Walker et al., 2004; Reuter et al., 2006). Subsequent *in vivo* experiments showed that a combination of nitazoxanide and albendazole reduced parasite weight by about 4 times in the murine model (Stettler et al., 2004). A good effect was observed in patients with disseminated cystic echinococcosis on affected soft tissue, muscles, or viscera, who received nitazoxanide additionally to the standard albendazole chemotherapy (with or without praziquantel). Nevertheless, nitazoxanide shows no effect on chronic and extensive body lesions (Perez-Molina et al., 2011).

A 3-month treatment course with the anticancer drugs daunorubicin, idarubicin, cytarabine, and fludarabine did not affect the size and contents of the echinococcus cysts in a patient suffering from acute leukemia and cystic echinococcosis of the liver. The antifungal agent amphotericin B was additionally applied within the chemotherapy schedule, but did not show parasitocidal activity against *E. granulosus* cysts either (Ali et al., 2005). However, *in vitro* data suggest that amphotericin B effectively inhibits the growth of *E. multilocularis* metacestodes (Reuter et al., 2003b). Amphotericin B is also able to halt parasite growth in *E. multilocularis*-infected patients and might therefore play a role as salvage treatment, when resistance or intolerance to benzimidazoles occurs (Reuter et al., 2003a).

The anthelmintic agent ivermectin was tested against *E. multilocularis* in hamsters with intraperitoneal inoculation of protoscolices, and in rats with transportal inoculation of protoscolices. The drug showed no effect in either case (Inaoka et al., 1987). In addition, *in vitro* results confirmed that ivermectin is also ineffective against *E. multilocularis* larvae (Reuter et al., 2006).

The spectrum of activity of antimalarials, such as mefloquine or the artemisinins, was also assessed against echinococcosis. Mefloquine presented a dose dependent activity against metacestodes *in vitro*, although a reduction of the parasite weight in *E. multilocularis*-infected mice was only achieved by intraperitoneal mefloquine administration and not with oral treatments (Kuster et al., 2011). Artesunate and dihydroartemisinin, however, had no effect against *E. multilocularis in vivo* (Spicher et al., 2008), despite excellent *in vitro* activity. Furthermore, *in vitro* incubation of *E. multilocularis* larvae with artemether did not induce destruction of parasite vesicles (Reuter et al., 2006).

Table 3
Drugs tested in clinical trials against the major cestodes (*Taenia* and *Echinococcus*).

Drug	Parasite	Number of patients	Dose	Outcome	References
Nitazoxanide	*T. saginata*	22	25 mg/kg	100% CR	Rossignol and Maisonneuve (1984)
	H. nana	18	50 mg/kg	100% CR	
	T. saginata	18 children 34 adults (niclosamide and praziquantel-resistant infections)	20 mg/kg p.o. (children 5–14 years); 500 mg twice daily for 3 days p.o. (> 14 years)	98% CR	Lateef et al. (2008)
	Echinococcus spp. (in combination with albendazole)	5	500 mg/12 hours for 3–24 months	40% improvement (2 patients improved)	Perez-Molina et al. (2011)
Mepacrine (quinacrine)	*T. saginata*	86	1 g p.o. or i.g.	94%	Koul et al. (2000)
Tribendimidine	*Taenia* spp.	15	200 mg p.o. single dose (children 5–14 years) 400 mg p.o. single dose (⩾15 years)	67% CR	Steinmann et al. (2008)
Paramomycin	*T. saginata*	145	1–5 days with 30–50 mg/kg	89–100% CR	Salem and el-Allaf (1969)
	H. nana	49	30 mg/kg single or double dose	90% CR	
Chlorhexidine gluconate	*E. granulosis*	30	0.04% in intracystic injection	100% death of cystic protoscolices	Topcu et al. (2009)

p.o denotes oral treatment, i.g. denotes treatment via a nasogastric tube, CR stands for "cure rate".

Ethanol (70–95%), hypertonic saline (15–30%) and cetrimide solution (0.5%) are considered to be scolicidal agents for PAIR treatment with relatively low risk according to the WHO (1996). Efforts were made to discover more potent scolicidal agents to reduce the recurrence rate following PAIR and surgical interventions. For instance, chlorhexidine gluconate, which is a commonly available, inexpensive, and non-toxic antiseptic agent, proved to be highly active at a concentration of 0.04% following intracystic injection (Topcu et al., 2009). Moreover, *in vitro* data confirm that intracystic albendazole sulfoxide injections at concentrations of 50–100 μg/ml are highly scolicidal and additional studies in rabbits indicate that this treatment lacks biliary and systemic toxicity (Erzurumlu et al., 1998; Adas et al., 2009). Recently, a water-soluble albendazole sulfoxide salt was developed (Bayverm®-PI, Bayer HealthCare), which enabled the preparation of a liquid dosing form and henceforth systemic and even intracystic injections. Importantly, systemic application circumvents the low oral absorption rate of albendazole and significantly elevates drug disposition (Lanusse et al., 1998). A proof of concept trial in sheep infected with *E. granulosus* ($n = 7$) was performed, which demonstrated that intracystic instillation without reaspiration of albendazole sulfoxide significantly decreased cyst size and lead to death of all protoscoleces and daughter cysts 6 months post-injection (Deger et al., 2000). Further studies in animals and human subjects are warranted to evaluate if this therapeutic approach could substitute the current lengthy oral albendazole therapy.

Albendazole and mebendazole are currently the recommended drugs for chemotherapy of echinococcosis; hence it is reasonable that other benzimidazole derivatives are investigated. For instance flubendazole induced 90% reduction in cyst weight compared to untreated mice infected with *E. granulosus*. This is particularly remarkable, as lower quantities of flubendazole were detected in plasma and within the cysts compared to albendazole treatments, suggesting a higher potency of flubendazole (Ceballos et al., 2011). Finally, it could be demonstrated that oxfendazole (60 mg/kg) alone and in combination with praziquantel was able to decrease protoscolex viability and reduce the diameter of liver and lung cysts in sheep naturally infected with *E. granulosus* following short-term treatment regimens (⩽6 weeks) (Gavidia et al., 2010). Notably, triclabendazole has shown potency *in vitro* and it would be interesting to see if it is as successful as the other benzimidazoles *in vivo* (Richter et al., 2013).

6. Conclusion

We have summarized drug repurposing efforts against a wide array of helminth infections. Drug repurposing is an important strategy, in particular for these neglected tropical diseases since drug discovery and development has languished in this field. Moreover, the time, effort and resources saved renders drug repurposing a smart and ethical choice, as it can result in faster and more affordable access to new medicines.

Several dozen compounds were identified by systematically searching the literature and presented in our review. This rather low number mirrors the challenges helminth drug discovery efforts still face. *In vitro* screens are often low throughput and cumbersome, as described for the *T. muris* assay (Wimmersberger et al., 2013). Furthermore, we lack adequate animal models; prominent examples are the two most important human filarials *O. volvulus* and *Wuchereria bancrofti*, and the problematic *L. loa*. As such, it is currently not possible to test drugs on these species directly *in vivo* and most testing is conducted with infection models from analogous animal filariasis infections, such as *O. ochengi* in cattle (Geary and Mackenzie, 2011).

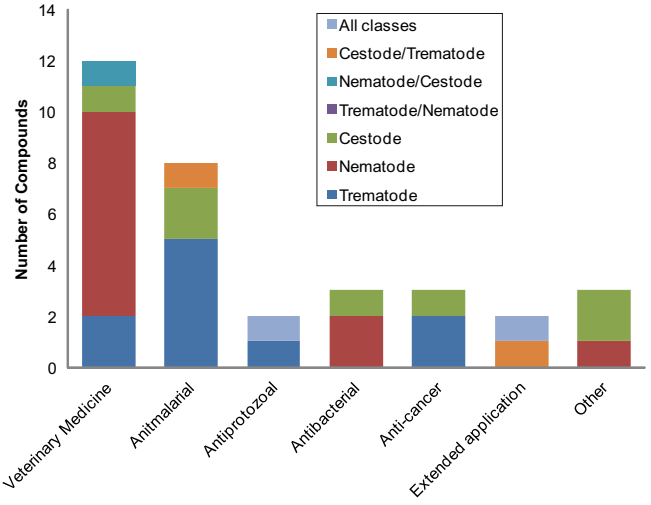

Figure 1. Sources of compounds for anthelmintic repurposing. A summary of the fields from which the repurposed drugs discussed in this review are sourced. Only successful drugs and drug candidates were included. "Extended applications" refers to drugs that were already anthelmintics but whose activity was discovered to extend to a broader range of helminth species.

Interestingly, only a few compound classes have been investigated and several compounds have been studied against different helminth species. Antimalarial and anticancer compounds were most widely studied, though most of the successful anthelmintic compounds still come from the antimalarial and veterinary fields. Though most repurposed drugs still come from veterinary anthelmintic R & D, gradually compounds from fields such as antiprotozoal and anticancer research are being increasingly investigated (Fig. 1). As mentioned in this review these drug classes were not randomly selected but rather based on biological features (flukes have the same blood-feeding characteristic as *Plasmodium* spp.) and possible drug targets (identification of select protein kinases as being essential to schistosome development) of these parasites. With the availability of genomes, e.g. *B. malayi* or the *L. loa* genome, it is the hope of many that compound libraries containing drugs' known modes of action can be matched *in silico* against helminth-specific gene targets, therefore providing potential drug candidates. In addition, unsurprisingly the benzimidazole class of compounds has been studied extensively. However, given that there is known cross-resistance between the various benzimidazoles in animal health, it is worth highlighting that a good clinical candidate arising from this group would rather replace albendazole and mebendazole than serve as backup.

Overall, disappointingly few compounds have been pursued into clinical testing, which does little to alleviate the dry anthelmintic pipelines. A notable exception however is the trichuricidal drug oxantel pamoate.

As public–private partnerships continue to expand, new compounds and compound libraries have been made openly accessible. For example, recently the Medicines for Malaria Venture made available an open-source library consisting of 200 drug-like and 200 probe-like compounds, which was screened against *S. mansoni in vitro* and *in vivo*. Though the *in vivo* results were moderate at best, it did provide two potential new scaffolds to of interest: the N,N′-diarylurea and 2,3-dianilinoquinoxaline derivatives (Ingram-Sieber et al., 2014). This is an example illustrating that closer collaborations between different research fields would be of great benefit in the field of drug discovery and development for helminth diseases. More of such collaborations are needed to take bench findings to the field and to turn field successes into affordable and useable medicines.

Conflict of interest

The authors state that they present no conflict of interest in writing this review.

Acknowledgments

This work was supported by the European Research Council (ERC-2013-CoG614739-A_HERO to G.P and J.K.), the Medicor Foundation (B.S) and the University of Basel Forschungsfonds (U.D.). The authors state that they present no conflict of interest in writing this review.

References

Abaza, H., El-Zayadi, A.R., Kabil, S.M., Rizk, H., 1998. Nitazoxanide in the treatment of patients with intestinal protozoan and helminthic infections: a report on 546 patients in Egypt. Curr. Ther. Res. 59, 116–121.

Abdul-Ghani, R.A., Loutfy, N., Hassan, A., 2009. Myrrh and trematodoses in Egypt: an overview of safety, efficacy and effectiveness profiles. Parasitol. Int. 58, 210–214.

Abdulla, M.H., Ruelas, D.S., Wolff, B., Snedecor, J., Lim, K.C., Xu, F., Renslo, A.R., Williams, J., McKerrow, J.H., Caffrey, C.R., 2009. Drug discovery for schistosomiasis: hit and lead compounds identified in a library of known drugs by medium-throughput phenotypic screening. PLoS Negl. Trop. Dis. 3, e478.

Abo-Madyan, A.A., Morsy, T.A., Motawea, S.M., Morsy, A.T., 2004. Clinical trial of Mirazid in treatment of human fascioliasis, Ezbet El-Bakly (Tamyia Center) Al-Fayoum Governorate. J. Egypt. Soc. Parasitol. 34, 807–818.

Adas, G., Arikan, S., Kemik, O., Oner, A., Sahip, N., Karatepe, O., 2009. Use of albendazole sulfoxide, albendazole sulfone, and combined solutions as scolicidal agents on hydatid cysts (*in vitro* study). World J. Gastroenterol. 15, 112–116.

Adenusi, A.A., Oke, A.O., Adenusi, A.O., 2003. Comparison of ivermectin and thiabendazole in the treatment of uncomplicated human *Strongyloides stercoralis* infection. Afr. J. Biotechnol. 2, 465–469.

Akaza, H., 2011. Combined androgen blockade for prostate cancer: review of efficacy, safety and cost-effectiveness. Cancer Sci. 102, 51–56.

Ali, R., Ozkalemkas, F., Ozkocaman, V., Ozcelik, T., Akalin, H., Ozkan, A., Altundal, Y., Tunali, A., 2005. Hydatid disease in acute leukemia: effect of anticancer treatment on echinococcosis. Microbes Infect. 7, 1073–1076.

Allarakhia, M., 2013. Open-source approaches for the repurposing of existing or failed candidate drugs: learning from and applying the lessons across diseases. Drug Des. Dev. Ther. 7, 753–766.

Altreuther, G., Radeloff, I., LeSueur, C., Schimmel, A., Krieger, K.J., 2009. Field evaluation of the efficacy and safety of emodepside plus praziquantel tablets (Profender tablets for dogs) against naturally acquired nematode and cestode infections in dogs. Parasitol. Res. 105 (Suppl 1), S23–29.

Andrews, K.T., Fisher, G., Skinner-Adams, T.S., 2014. Drug repurposing and human parasitic protozoan diseases. Int. J. Parasitol. Drugs Drug. Resist. 4, 95–111.

Andrews, P., Thomas, H., Pohlke, R., Seubert, J., 1983. Praziquantel. Med. Res. Rev. 3, 147–200.

Anonymous, 2009. Global programme to eliminate lymphatic filariasis. Wkly Epidemiol. Rec. 84, 437–444.

Anonymous, 2012. Soil-transmitted helminthiases: number of children treated in 2010. Wkly Epidemiol. Rec. 87, 225–232.

Anonymous, 2014. Preventive chemotherapy: planning, requesting medicines, and reporting. Wkly Epidemiol. Rec. 89, 61–71.

Armson, A., Cunningham, G.A., Grubb, W.B., Mendis, A.H., 1995. Murine strongyloidiasis: the effects of cyclosporin A and thiabendazole administered singly and in combination. Int. J. Parasitol. 25, 533–535.

Awadzi, K., Schulz-Key, H., Howells, R.E., Haddock, D.R., Gilles, H.M., 1982. The chemotherapy of onchocerciasis VIII Levamisole and its combination with the benzimidazoles. Ann. Trop. Med. Parasitol. 76, 459–473.

Awadzi, K., Edwards, G., Opoku, N.O., Ardrey, A.E., Favager, S., Addy, E.T., Attah, S.K., Yamuah, L.K., Quartey, B.T., 2004. The safety, tolerability and pharmacokinetics of levamisole alone, levamisole plus ivermectin, and levamisole plus albendazole, and their efficacy against *Onchocerca volvulus*. Ann. Trop. Med. Parasitol. 98, 595–614.

Awadzi, K., Opoku, N.O., Attah, S.K., Lazdins-Helds, J., Kuesel, A.C., 2014. A randomized, single-ascending-dose, ivermectin-controlled, double-blind study of moxidectin on *Onchocerca volvulus* infection. PLoS Negl. Trop. Dis. 8 (6), e2953.

Awasthi, A., Razzak, M., Al-Kassas, R., Harvey, J., Garg, S., 2013. Analytical profile of moxidectin. Profiles of drug substances, excipients, and related methodology 38, 315–366.

Babalola, O.E., 2011. Ocular onchocerciasis: current management and future prospects. Clin. Ophthalmol. 5, 1479–1491.

Basra, A., Mombo-Ngoma, G., Melser, M.C., Diop, D.A., Wurbel, H., Mackanga, J.R., Furstenau, M., Zoleko, R.M., Adegnika, A.A., Gonzalez, R., Menendez, C., Kremsner, P.G., Ramharter, M., 2013. Efficacy of mefloquine intermittent preventive treatment in pregnancy against *Schistosoma haematobium* infection in Gabon: a nested randomized controlled assessor-blinded clinical trial. Clin. Infect. Dis. 56, e68–75.

Bauer, C., Conraths, F.J., 1994. Comparative efficacy of moxidectin and mebendazole against gastrointestinal nematodes in experimentally infected lambs. Vet. Rec. 135, 136–138.

Beckman, S., Grevelding, C.G., 2010. Imatinib has a fatal impact on morphology, pairing stability and survival of adult *Schistosoma mansoni in vitro*. Int. J. Parasitol. 40, 521–526.

Bisoffi, Z., Buonfrate, D., Angheben, A., Boscolo, M., Anselmi, M., Marocco, S., Monteiro, G., Gobbo, M., Bisoffi, G., Gobbi, F., 2011. Randomized clinical trial on ivermectin versus thiabendazole for the treatment of strongyloidiasis. PLoS Negl. Trop. Dis. 5, e1254.

Bisoffi, Z., Buonfrate, D., Montresor, A., Requena-Mendez, A., Munoz, J., Krolewiecki, A.J., Gotuzzo, E., Mena, M.A., Chiodini, P.L., Anselmi, M., Moreira, J., Albonico, M., 2013. *Strongyloides stercoralis*: a plea for action. PLoS Negl. Trop. Dis. 7, e2214.

Blagburn, B.L., Hendrix, C.M., Lindsay, D.S., Vaughan, J.L., Hepler, D.I., Wright, J.C., 1992. Efficacy of milbemycin oxime against naturally acquired or experimentally induced *Ancylostoma* spp. and *Trichuris vulpis* infections in dogs. Am. J. Vet. Res. 53, 513–516.

Botros, S.S., El-Lakkany, N.M., Badawy, A.A., Mahmoud, S.S., Ebeid, F.A., Fenwick, A., 2009. Mirazid shows insignificant activity against ovine fascioliasis. Ann. Trop. Med. Parasitol. 103, 605–616.

Brennan, G.P., Fairweather, I., Trudgett, A., Hoey, E., McCoy, McConville, M., Meaney, M., Robinson, M., McFerran, N., Ryan, L., Lanusse, C., Mottier, L., Alvarez, L., Solana, H., Virkel, G., Brophy, P.M., 2007. Understanding triclabendazole resistance. Exp. Mol. Pathol. 82, 104–109.

Bruch, K., Haas, J., 1976. Effectiveness of single doses of Fenbendazole Hoe 88I against *Ascaris*, hookworm and *Trichuris* in man. Ann. Trop. Med. Parasitol. 70, 205–211.

Brunetti, E., Kern, P., Vuitton, D.A., 2010. Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 114, 1–16.

Brunetti, E., White Jr., A.C., 2012. Cestode infestations: hydatid disease and cysticercosis. Infect. Dis. Clin. North Am. 26, 421–435.

Bueding, E., Hawkins, J., Cha, Y.N., 1981. Antischistosomal effects of cyclosporin A. Agents Actions 11, 380–383.

Bunnag, D., Harinasuta, T., Viravan, C., Jarupakorn, V., Chindanond, D., Desakorn, V., 1980. Clinical trial of flubendazole on hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections. Southeast Asian. J. Trop. Med. Public Health 11, 363–366.

Bygott, J.M., Chiodini, P.L., 2009. Praziquantel: neglected drug? Ineffective treatment? Or therapeutic choice in cystic hydatid disease? Acta Trop. 111, 95–101.

Caffrey, C.R., 2007. Chemotherapy of schistosomiasis: present and future. Curr. Opin. Chem. Biol. 11, 433–439.

Carpio, A., 2002. Neurocysticercosis: an update. Lancet Infect. Dis. 2, 751–762.

Catton, D.G., Van Schalkwyk, P.C., 2003. The efficacy of two anthelmintics against ascarids and hookworms in naturally infected cats. Parasitol. Res. 90 (Suppl 3), S144–145.

Ceballos, L., Elissondo, M., Bruni, S.S., Denegri, G., Alvarez, L., Lanusse, C., 2009. Flubendazole in cystic echinococcosis therapy: pharmaco-parasitological evaluation in mice. Parasitol. Int. 58, 354–358.

Ceballos, L., Elissondo, C., Sanchez Bruni, S., Denegri, G., Lanusse, C., Alvarez, L., 2011. Comparative performances of flubendazole and albendazole in cystic echinococcosis: *ex vivo* activity, plasma/cyst disposition, and efficacy in infected mice. Antimicrob. Agents Chemother. 55, 5861–5867.

Ceballos, L., Moreno, L., Torrado, J.J., Lanusse, C., Alvarez, L., 2012. Exploring flubendazole formulations for use in sheep. Pharmacokinetic evaluation of a cyclodextrin-based solution. BMC Vet. Res. 8, 71.

Cobo, F., Yarnoz, C., Sesma, B., Fraile, P., Aizcorbe, M., Trujillo, R., Diaz-de-Liano, A., Ciga, M.A., 1998. Albendazole plus praziquantel versus albendazole alone as a pre-operative treatment in intra-abdominal hydatisosis caused by *Echinococcus granulosus*. Trop. Med. Int. Health 3, 462–466.

Cohen, D.J., Loertscher, R., Rubin, M.F., Tilney, N.L., Carpenter, C.B., Strom, T.B., 1984. Cyclosporine: a new immunosuppressive agent for organ transplantation. Annals Intern. Med. 101, 667–682.

Coles, G.C., Giordano-Fenton, D.J., Tritschler 2nd, J.P., 1994. Efficacy of moxidectin against nematodes in naturally infected sheep. Vet. Rec. 135, 38–39.

Cotreau, M.M., Warren, S., Ryan, J.L., Fleckenstein, L., Vanapalli, S.R., Brown, K.R., Rock, D., Chen, C.Y., Schwertschlag, U.S., 2003. The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. J. Clin. Pharmacol. 43, 1108–1115.

Coulibaly, Y.I., Dembele, B., Diallo, A.A., Lipner, E.M., Doumbia, S.S., Coulibaly, S.Y., Konate, S., Diallo, D.A., Yalcouye, D., Kubofcik, J., Doumbo, O.K., Traore, A.K., Keita, A.D., Fay, M.P., Traore, S.F., Nutman, T.B., Klion, A.D., 2009. A randomized trial of doxycycline for *Mansonella perstans* infection. New Eng. J. Med. 361, 1448–1458.

Davidson, R.N., den Boer, M., Ritmeijer, K., 2009. Paromomycin. Trans. R. Soc. Trop. Med. Hyg. 103, 653–660.

de Silva, D.G., Lionel, N.D., Jayatilleka, S.M., 1984. Flubendazole in the treatment of *Ascaris lumbricoides* and *Trichuris trichiura*: a comparison of two different regimens with single-dose. Ceylon Med. J. 29, 199–203.

Debrah, A.Y., Mand, S., Marfo-Debrekyei, Y., Batsa, L., Pfarr, K., Buttner, M., Adjei, O., Buttner, D., Hoerauf, A., 2007. Macrofilaricidal effect of 4 weeks of treatment

with doxycycline on *Wuchereria bancrofti*. Trop. Med. Int. Health 12, 1433–1441.
Debrah, A.Y., Mand, S., Marfo-Debrekyei, Y., Batsa, L., Pfarr, K., Lawson, B., Taylor, M., Adjei, O., Hoerauf, A., 2009. Reduction in levels of plasma vascular endothelial growth factor-A and improvement in hydrocele patients by targeting endosymbiotic *Wolbachia* sp. in *Wuchereria bancrofti* with doxycycline. Am. J. Trop. Med. Hyg. 80, 956–963.
Deger, E., Hokelek, M., Deger, B.A., Tutar, E., Asil, M., Pakdemirli, E., 2000. A new therapeutic approach for the treatment of cystic echinococcosis: percutaneous albendazole sulphoxide injection without reaspiration. Am. J. Gastroenterol. 95, 248–254.
den Hollander, P., Savage, M.I., Brown, P.H., 2013. Targeted therapy for breast cancer prevention. Front. Oncol. 3, 250.
Diaz, E., Mondragon, J., Ramirez, E., Bernal, R., 2003. Epidemiology and control of intestinal parasites with nitazoxanide in children in Mexico. Am. J. Trop. Med. Hyg. 68, 384–385.
Dissous, C., Grevelding, C.G., 2011. Piggy-backing the concept of cancer drugs for schistosomiasis treatment: a tangible perspective? Trends Parasitol. 27, 59–66.
Dominguez-Vazquez, A., Taylor, H.R., Greene, B.M., Ruvalcaba-Macias, A.M., Rivas-Alcala, A.R., Murphy, R.P., Beltran-Hernandez, F., 1983. Comparison of flubendazole and diethylcarbamazine in treatment of onchocerciasis. Lancet 1, 139–143.
Dorlo, T.P., Balasegaram, M., Beijnen, J.H., de Vries, P.J., 2012. Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. J. Antimicrob. Chemother. 67, 2576–2597.
Dreyer, G., Addiss, D., Williamson, J., Noroes, J., 2006. Efficacy of co-administered diethylcarbamazine and albendazole against adult *Wuchereria bancrofti*. Trans. R. Soc. Trop. Med. Hyg. 100, 1118–1125.
Eissa, M.M., El-Azzouni, M.Z., Amer, E.I., Baddour, N.M., 2011a. Miltefosine, a promising novel agent for schistosomiasis mansoni. Int. J. Parasitol. 41, 235–242.
Eissa, M.M., El Bardicy, S., Tadros, M., 2011b. Bioactivity of miltefosine against aquatic stages of *Schistosoma mansoni, Schistosoma haematobium* and their snail hosts, supported by scanning electron microscopy. Parasite Vector 4, 73.
El Bialy, S.A., Taman, A., El-Beshbishi, S.N., Mansour, B., El-Malky, M., Bayoumi, W.A., Essa, H.M., 2013. Effect of a novel benzimidazole derivative in experimental *Schistosoma mansoni* infection. Parasitol. Res. 112, 4221–4229.
Erzurumlu, K., Hokelek, M., Baris, S., Sahin, M., Birinci, A., Amanvermez, R., Tac, K., 1998. Effect of albendazole sulfoxide solution on the scolices and the hepatobiliary system. Eur. Surg. Res. 30, 433–438.
Escobedo, G., Palacios-Arreola, M.I., Olivos, A., Lopez-Griego, L., Morales-Montor, J., 2013. Tamoxifen treatment in hamsters induces protection during taeniosis by *Taenia solium*. BioMed Res. Int. 2013, 280496.
Favennec, L., Jave Ortiz, J., Gargala, G., Lopez Chegne, N., Ayoub, A., Rossignol, J.F., 2003. Double-blind, randomized, placebo-controlled study of nitazoxanide in the treatment of fascioliasis in adults and children from northern Peru. Aliment. Pharmacol. Ther. 17, 265–270.
Franz, M., Zahner, H., Benten, P., 1990. Fine-structure alterations in female *Brugia malayi* and *Litomosoides carinii* after *in vivo* treatment with flubendazole. Parasitol. Res. 76, 401–405.
Fürst, T., Duthaler, U., Sripa, B., Utzinger, J., Keiser, J., 2012. Trematode infections: liver and lung flukes. Infect. Dis. Clin. North Am. 26, 399–419.
Gann, P.H., Neva, F.A., Gam, A.A., 1994. A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. J. Infect. Dis. 169, 1076–1079.
Garcia, E.G., 1976. Treatment for trichuriasis with oxantel. Am. J. Trop. Med. Hyg. 25, 914–915.
Garcia, H.H., Lescano, A.G., Lanchote, V.L., Pretell, E.J., Gonzales, I., Bustos, J.A., Takayanagui, O.M., Bonato, P.S., Horton, J., Saavedra, H., Gonzalez, A.E., Gilman, R.H., 2011. Cysticercosis working group in Peru. Pharmacokinetics of combined treatment with praziquantel and albendazole in neurocysticercosis. Br. J. Clin. Pharmacol. 72, 77–84.
Gardner, J.M., Grantham-McGregor, S., Baddeley, A., 1996. *Trichuris trichiura* infection and cognitive function in Jamaican school children. Ann. Trop. Med. Parasitol. 90, 55–63.
Gavidia, C.M., Gonzalez, A.E., Barron, E.A., Ninaquispe, B., Llamosas, M., Verastegui, M.R., Robinson, C., Gilman, R.H., 2010. Evaluation of oxfendazole, praziquantel and albendazole against cystic echinococcosis: a randomized clinical trial in naturally infected sheep. PLoS Negl. Trop. Dis. 4, e616.
Gayen, P., Nayak, A., Saini, P., Mukherjee, N., Maitra, S., Sarkar, P., Sinha Babu, S.P., 2013. A double-blind controlled field trial of doxycycline and albendazole in combination for the treatment of bancroftian filariasis in India. Acta Trop. 125, 150–156.
Geary, T.G., Mackenzie, C.D., 2011. Progress and challenges in the discovery of macrofilaricidal drugs. Expert Rev. Anti Infect. Ther. 9, 681–695.
Greaves, D., Coggle, S., Pollard, C., Aliyu, S.H., Moore, E.M., 2013. *Strongyloides stercoralis* infection. BMJ 347, f4610.
Gryseels, B., 2012. Schistosomiasis. Infect. Dis. Clin. North Am. 26, 383–397.
Harder, A., von Samson-Himmelstjerna, G., 2002. Cyclooctadepsipeptides – a new class of anthelmintically active compounds. Parasitol. Res. 88, 481–488.
Harder, A., Schmitt-Wrede, H.P., Krucken, J., Marinovski, P., Wunderlich, F., Willson, J., Amliwala, K., Holden-Dye, L., Walker, R., 2003. Cyclooctadepsipeptides–an anthelmintically active class of compounds exhibiting a novel mode of action. Int. J. Antimicrob. Agents 22, 318–331.
Hemphill, A., Mueller, J., Esposito, M., 2006. Nitazoxanide, a broad-spectrum thiazolide anti-infective agent for the treatment of gastrointestinal infections. Expert Opin. Pharmacother. 7, 953–964.
Hien, T.T., Truong, N.T., Minh, N.H., Dat, H.D., Dung, N.T., Hue, N.T., Dung, T.K., Tuan, P.Q., Campbell, J.I., Farrar, J.J., Day, J.N., 2008. A randomized controlled pilot study of artesunate versus triclabendazole for human fascioliasis in central Vietnam. Am. J. Trop. Med. Hyg. 78, 388–392.
Ho, W.E., Peh, H.Y., Chan, T.K., Wong, W.S., 2014. Artemisinins: pharmacological actions beyond anti-malarial. Pharmacol. Ther. 142, 126–139.
Hoerauf, A., Mand, S., Volkmann, L., Buttner, M., Marfo-Debrekyei, Y., Taylor, M., Adjei, O., Buttner, D.W., 2003. Doxycycline in the treatment of human onchocerciasis: kinetics of *Wolbachia* endobacteria reduction and of inhibition of embryogenesis in female *Onchocerca* worms. Microb. Infect. 5, 261–273.
Hoerauf, A., Marfo-Debrekyei, Y., Buttner, M., Debrah, A.Y., Konadu, P., Mand, S., Adjei, O., Buttner, D.W., 2008a. Effects of 6-week azithromycin treatment on the *Wolbachia endobacteria* of *Onchocerca volvulus*. Parasitol. Res. 103, 279–286.
Hoerauf, A., Specht, S., Buttner, M., Pfarr, K., Mand, S., Fimmers, R., Marfo-Debrekyei, Y., Konadu, P., Debrah, A.Y., Bandi, C., Brattig, N., Albers, A., Larbi, J., Batsa, L., Taylor, M.J., Adjei, O., Buttner, D.W., 2008b. *Wolbachia* endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study. Med. Microbiol. Immunol. 197, 295–311.
Holmstedt, B., Nordgren, I., Sandoz, M., Sundwall, A., 1978. Metrifonate. Summary of toxicological and pharmacological information available. Arch. Toxicol. 41, 3–29.
Hotez, P.J., Molyneux, D.H., Fenwick, A., Ottesen, E., Ehrlich Sachs, S., Sachs, J.D., 2006. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med. 3, e102.
Huang, Y.X., Zhou, J.X., Xue, Z.Q., Wu, Y.X., Chen, J.Y., Wu, H.Z., Ji, M.H., Shen, Y.P., Cao, G.Q., Wu, Z.X., et al., 1990. Clinical observations on the treatment of hookworm, Ascaris and Trichuris infection with oxibendazole. Chin. J. Parasitol. Parasit. Dis. 8, 100–103.
Inaoka, T., Nakao, M., Ohnishi, K., Kutsumi, H., 1987. Experimental therapy in Chinese hamsters and rats infected with larval *Echinococcus multilocularis* by using mebendazole, albendazole and ivermectin with brief review of chemotherapy of human multilocular echinococcosis. Hokkaido J Med Sci 62, 54–67.
Ingold, K., Bigler, P., Thormann, W., Cavaliero, T., Gottstein, B., Hemphill, A., 1999. Efficacies of albendazole sulfoxide and albendazole sulfone against *in vitro*-cultivated *Echinococcus multilocularis* metacestodes. Antimicrob. Agents Chemother. 43, 1052–1061.
Ingram, K., Ellis, W., Keiser, J., 2012a. Antischistosomal activities of mefloquine-related arylmethanols. Antimicrob. Agents Chemother. 56, 3207–3215.
Ingram, K., Schiaffo, C.E., Sittiwong, W., Benner, E., Dussault, P.H., Keiser, J., 2012b. *In vitro* and *in vivo* activity of 3-alkoxy-1,2-dioxolanes against *Schistosoma mansoni*. J. Antimicrob. Ther. 67, 1979–1986.
Ingram-Sieber, K., Cowan, N., Panic, G., Vargas, M., Mansour, N.R., Bickle, Q.D., Wells, T.N., Spangenberg, T., Keiser, J., 2014. Orally active antischistosomal early leads identified from the open access malaria box. PLoS Negl. Trop. Dis. 8, e2610.
Jones, R.M., Logan, N.B., Weatherley, A.J., Little, A.S., Smothers, C.D., 1993. Activity of doramectin against nematode endoparasites of cattle. Vet. Parasitol. 49, 27–37.
Juan, J.O., Lopez Chegne, N., Gargala, G., Favennec, L., 2002. Comparative clinical studies of nitazoxanide, albendazole and praziquantel in the treatment of ascariasis, trichuriasis and hymenolepiasis in children from Peru. Trans. R. Soc. Trop. Med. Hyg. 96, 193–196.
Kamgno, J., Pion, S.D., Tejiokem, M.C., Twum-Danso, N.A., Thylefors, B., Boussinesq, M., 2007. Randomized, controlled, double-blind trial with ivermectin on *Loa loa* microfilaraemia: efficacy of a low dose (approximately 25 microg/kg) versus current standard dose (150 microg/kg). Trans. R. Soc. Trop. Med. Hyg. 101, 777–785.
Kamgno, J., Djomo, P.N., Pion, S.D., Thylefors, B., Boussinesq, M., 2010. A controlled trial to assess the effect of quinine, chloroquine, amodiaquine, and artesunate on *Loa loa* microfilaremia. Am. J. Trop. Med. Hyg. 82, 379–385.
Kan, S.P., 1983. The anthelmintic effects of flubendazole on *Trichuris trichiura* and *Ascaris lumbricoides*. Trans. R. Soc. Trop. Med. Hyg. 77, 668–670.
Katiyar, D., Singh, L.K., 2011. Filariasis: current status, treatment and recent advances in drug development. Curr. Med. Chem. 18, 2174–2185.
Katz, N., Couto, F.F., Araujo, N., 2013. Imatinib activity on *Schistosoma mansoni*. Mem. Inst. Oswaldo Cruz 108, 850–853.
Keiser, J., Utzinger, J., 2004. Chemotherapy for major food-borne trematodes: a review. Expert Opin. Pharmacother. 5, 1711–1726.
Keiser, J., Utzinger, J., 2007a. Advances in the discovery and development of novel trematocidal drugs. Expert Opin. Drug Discov. 2, 9–23.
Keiser, J., Utzinger, J., 2007b. Artemisinins and synthetic trioxolanes in the treatment of helminth infections. Curr. Opin. Infect. Dis. 20, 605–612.
Keiser, J., Utzinger, J., 2007c. Food-borne trematodiasis: current chemotherapy and advances with artemisinins and synthetic trioxolanes. Trends Parasitol. 23, 555–562.
Keiser, J., Utzinger, J., 2008. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. JAMA 299, 1937–1948.
Keiser, J., Utzinger, J., 2010. The drugs we have and the drugs we need against major helminth infections. Adv. Parasitol. 73, 197–230.
Keiser, J., Utzinger, J., 2012. Antimalarials in the treatment of schistosomiasis. Curr. Pharm. Des. 18, 3531–3538.
Keiser, J., Engels, D., Büscher, G., Utzinger, J., 2005. Triclabendazole for the treatment of fascioliasis and paragonimiasis. Expert Opin. Investig. Drugs 14, 1513–1526.

Keiser, J., Brun, R., Fried, B., Utzinger, J., 2006a. Trematocidal activity of praziquantel and artemisinin derivatives: *in vitro* and *in vivo* investigations with adult *Echinostoma caproni*. Antimicrob. Agents Chemother. 50, 803–805.

Keiser, J., Utzinger, J., Tanner, M., Dong, Y., Vennerstrom, J.L., 2006b. The synthetic peroxide OZ78 is effective against *Echinostoma caproni* and *Fasciola hepatica*. J. Antimicrob. Chemother. 58, 1193–1197.

Keiser, J., Xiao, S.H., Tanner, M., Utzinger, J., 2006c. Artesunate and artemether are effective fasciolicides in the rat model and *in vitro*. J. Antimicrob. Chemother. 57, 1139–1145.

Keiser, J., Xiao, S.H., Xue, J., Chan, Z.S., Odermatt, P., Tesana, S., Tanner, M., Utzinger, J., 2006d. Effect of artesunate and artemether against *Clonorchis sinensis* and *Opisthorchis viverrini* in rodent models. Int. J. Antimicrob. Agents 28, 370–373.

Keiser, J., Utzinger, J., Vennerstrom, J.L., Dong, Y., Brennan, G., Fairweather, I., 2007a. Activity of artemether and OZ78 against triclabendazole-resistant *Fasciola hepatica*. Trans. R. Soc. Trop. Med. Hyg. 101, 1219–1222.

Keiser, J., Xiao, S.H., Chollet, J., Tanner, M., Utzinger, J., 2007b. Evaluation of the *in vivo* activity of tribendimidine against *Schistosoma mansoni*, *Fasciola hepatica*, *Clonorchis sinensis*, and *Opisthorchis viverrini*. Antimicrob. Agents Chemother. 51, 1096–1098.

Keiser, J., Rinaldi, L., Veneziano, V., Mezzino, L., Tanner, M., Utzinger, J., Cringoli, G., 2008a. Efficacy and safety of artemether against a natural *Fasciola hepatica* infection in sheep. Parasitol. Res. 103, 517–522.

Keiser, J., Thiemann, K., Endriss, Y., Utzinger, J., 2008b. *Strongyloides ratti*: *in vitro* and *in vivo* activity of tribendimidine. PLoS Negl. Trop. Dis., e201.

Keiser, J., Odermatt, P., Tesana, S., 2009a. Dose-response relationships and tegumental surface alterations in *Opisthorchis viverrini* following treatment with mefloquine *in vivo* and *in vitro*. Parasitol. Res. 105, 261–266.

Keiser, J., Xiao, S.H., Smith, T.A., Utzinger, J., 2009b. Combination chemotherapy against *Clonorchis sinensis*: experiments with artemether, artesunate, OZ78, praziquantel, and tribendimidine in a rat model. Antimicrob. Agents Chemother. 53, 3770–3776.

Keiser, J., Duthaler, U., Utzinger, J., 2010a. Update on the diagnosis and treatment of food-borne trematode infections. Curr. Opin. Infect. Dis. 23, 513–520.

Keiser, J., Kirchhofer, C., Haschke, M., Huwyler, J., Dong, Y., Vennerstrom, J.L., Vanhoff, K., Kaminsky, R., Malikides, N., 2010b. Efficacy, safety and pharmacokinetics of 1,2,4-trioxolane OZ78 against an experimental infection with *Fasciola hepatica* in sheep. Vet. Parasitol. 173, 228–235.

Keiser, J., N'Guessan, N.A., Adoubryn, K.D., Silue, K.D., Vounatsou, P., Hatz, C., Utzinger, J., N'Goran, E.K., 2010c. Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, and praziquantel against *Schistosoma haematobium*: randomized, exploratory open-label trial. Clin. Infect. Dis. 50, 1205–1213.

Keiser, J., Vargas, M., Vennerstrom, J.L., 2010d. Activity of antiandrogens against juvenile and adult *Schistosoma mansoni* in mice. J. Antimicrob. Chemother. 65, 1991–1995.

Keiser, J., Veneziano, V., Rinaldi, L., Mezzino, L., Duthaler, U., Cringoli, G., 2010e. Anthelmintic activity of artesunate against *Fasciola hepatica* in naturally infected sheep. Res. Vet. Sci. 88, 107–110.

Keiser, J., Sayed, H., El-Ghanam, M., Sabry, H., Anani, S., El-Wakeel, A., Hatz, C., Utzinger, J., El-Din, S.S., El-Maadawy, W., Botros, S., 2011. Efficacy and safety of artemether in the treatment of chronic fascioliasis in Egypt: exploratory phase-2 trials. PLoS Negl. Trop. Dis. 5, e1285.

Keiser, J., Ingram, K., Vargas, M., Chollet, J., Wang, X., Dong, Y., Vennerstrom, J.L., 2012a. *In vivo* activity of aryl ozonides against *Schistosoma* species. Antimicrob. Agents Chemother. 56, 1090–1092.

Keiser, J., Tritten, L., Adelfio, R., Vargas, M., 2012b. Effect of combinations of marketed human anthelmintic drugs against *Trichuris muris in vitro* and *in vivo*. Parasite Vectors 5, 292.

Keiser, J., Adelfio, R., Vargas, M., Odermatt, P., Tesana, S., 2013a. Activity of tribendimidine and praziquantel combination therapy against the liver fluke *Opisthorchis viverrini in vitro* and *in vivo*. J. Helminthol. 87, 252–256.

Keiser, J., Tritten, L., Silbereisen, A., Speich, B., Adelfio, R., Vargas, M., 2013b. Activity of oxantel pamoate monotherapy and combination chemotherapy against *Trichuris muris* and hookworms: revival of an old drug. PLoS Negl. Trop. Dis. 7, e2119.

Kern, P., 2006. Medical treatment of echinococcosis under the guidance of Good Clinical Practice (GCP/ICH). Parasitol. Int. 55 (Suppl.), S273–S282.

Knopp, S., Steinmann, P., Hatz, C., Keiser, J., Utzinger, J., 2012a. Nematode infections: filariases. Infect. Dis. Clin. North Am. 26, 359–381.

Knopp, S., Steinmann, P., Keiser, J., Utzinger, J., 2012b. Nematode infections: soil-transmitted helminths and trichinella. Infect. Dis. Clin. North Am. 26, 341–358.

Knopp, S., Becker, S.L., Ingram, K.J., Keiser, J., Utzinger, J., 2013. Diagnosis and treatment of schistosomiasis in children in the era of intensified control. Expert Rev. Anti. Infect. Ther. 11, 1237–1258.

Koul, P.A., Wahid, A., Bhat, M.H., Wani, J.I., Sofi, B.A., 2000. Mepacrine therapy in niclosamide resistant taeniasis. J. Assoc. Physicians India 48, 402–403.

Kulke, D., Krucken, J., Welz, C., von Samson-Himmelstjerna, G., Harder, A., 2012. *In vivo* efficacy of the anthelmintic tribendimidine against the cestode *Hymenolepis microstoma* in a controlled laboratory trial. Acta Trop. 123, 78–84.

Kulke, D., Krücken, J., Harder, A., Samson-Himmelstjerna, G., 2014. Efficacy of cyclooctadepsipeptides and aminophenylamides against larval, immature and mature adult stages of a parasitologically characterized trichurosis model in mice. PLoS Negl. Trop. Dis. 8 (2), e2698.

Kuster, T., Stadelmann, B., Hermann, C., Scholl, S., Keiser, J., Hemphill, A., 2011. *In vitro* and *in vivo* efficacies of mefloquine-based treatment against alveolar echinococcosis. Antimicrob. Agents Chemother. 55, 713–721.

Lanusse, C.E., Virkel, G.L., Sanchez, S.F., Alvarez, L.I., Lifschitz, A.L., Imperiale, F., Monfrinotti, A., 1998. Ricobendazole kinetics and availability following subcutaneous administration of a novel injectable formulation to calves. Res. Vet. Sci. 65, 5–10.

Lateef, M., Zargar, S.A., Khan, A.R., Nazir, M., Shoukat, A., 2008. Successful treatment of niclosamide and praziquantel-resistant beef tapeworm infection with nitazoxanide. Int. J. Infect. Dis. IJID 12, 80–82.

Lee, E.L., Iyngkaran, N., Grieve, A.W., Robinson, M.J., Dissanaike, A.S., 1976. Therapeutic evaluation of oxantel pamoate (1,4,5,6-tetrahydro-1-methyl-2-[trans-3-hydroxystyryl] pyrimidine pamoate) in severe *Trichuris trichiura* infection. Am. J. Trop. Med. Hyg. 25, 563–567.

Lee, S.H., Lim, J.K., 1978. Comparative study of effect of oxantel-pyrantel suspension and mebendazole in mixed infections with *Ascaris* and *Trichuris*. Drugs 15, 94–98.

Li, H.J., Wang, W., Qu, G.L., Tao, Y.H., Xing, Y.T., Li, Y.Z., Wei, J.Y., Dai, J.R., Liang, Y.S., 2011. *In vivo* activity of dihydroartemisinin against *Schistosoma japonicum*. Ann. Trop. Med. Parasitol. 105, 181–185.

Li, H.J., Wang, W., Qu, G.L., Li, Y.Z., Tao, Y.H., Xing, Y.T., Wang, X.T., Dai, Y., Wei, J.Y., Dai, J.R., Coles, G.C., Liang, Y.S., 2012. Effect of the *in vivo* activity of dihydroartemisinin against *Schistosoma mansoni* infection in mice. Parasitol. Res. 110, 1727–1732.

Li, H.J., Xu, F.L., Wang, Y.H., Yi, Z.J., Wang, W., 2014. Dihydroartemisinin: a new story of an old drug against *Schistosoma mansoni* infection. Parasitol. Res. 113, 239–241.

Link, H., Stohler, H.R., 1984. 3-Arylhydantoine, eine Substanzklasse mit schistosomizider Wirkung. Eur. J. Med. Chem. 19, 261–265.

Liu, R., Dong, H.F., Guo, Y., Zhao, Q.P., Jiang, M.S., 2011. Efficacy of praziquantel and artemisinin derivatives for the treatment and prevention of human schistosomiasis: a systematic review and meta-analysis. Parasite Vectors 4, 201.

Lumaret, J.P., Errouissi, F., Floate, K., Rombke, J., Wardhaugh, K., 2012. A review on the toxicity and non-target effects of macrocyclic lactones in terrestrial and aquatic environments. Curr. Pharm. Biotechnol. 13, 1004–1060.

Lyons, E.T., Tolliver, S.C., Collins, S.S., 2006. Field studies on endoparasites of thoroughbred foals on seven farms in central Kentucky in 2004. Parasitol. Res. 98, 496–500.

Mackenzie, C.D., Geary, T.G., 2011. Flubendazole: a candidate macrofilaricide for lymphatic filariasis and onchocerciasis field programs. Expert Rev. Anti Infect. Ther. 9, 497–501.

Mand, S., Pfarr, K., Sahoo, P.K., Satapathy, A.K., Specht, S., Klarmann, U., Debrah, A.Y., Ravindran, B., Hoerauf, A., 2009. Macrofilaricidal activity and amelioration of lymphatic pathology in bancroftian filariasis after 3 weeks of doxycycline followed by single-dose diethylcarbamazine. Am. J. Trop. Med. Hyg. 81, 702–711.

Mand, S., Debrah, A.Y., Klarmann, U., Batsa, L., Marfo-Debrekyei, Y., Kwarteng, A., Specht, S., Belda-Domene, A., Fimmers, R., Taylor, M., Adjei, O., Hoerauf, A., 2012. Doxycycline improves filarial lymphedema independent of active filarial infection: a randomized controlled trial. Clin. Infect. Dis. 55, 621–630.

Mansour-Ghanaei, F., Shafaghi, A., Fallah, M., 2003. The effect of metronidazole in treating human fascioliasis. Med. Sci. Monit. 9, Pi127–Pi130.

Masud, H., Qureshi, T.Q., Dukley, M., 2009. Effects of Ivermectin with and without doxycycline on clinical symptoms of onchocerciasis. J. Coll. Physicians Surg. Pak. 19, 34–38.

McMahon, J.E., 1981. Chemotherapy with diethylcarbamazine and levamisole in Bancroftian filariasis. Tropenmedizin Parasitol. 32, 250–252.

Meister, I., Duthaler, U., Huwyler, J., Rinaldi, L., Bosco, A., Cringoli, G., Keiser, J., 2013. Efficacy and pharmacokinetics of OZ78 and MT04 against a natural infection with *Fasciola hepatica* in sheep. Vet. Parasitol. 198, 102–110.

Mossallam, S.F., Ali, S.M., El Zawawy, L.A., Said, D.E., 2007. The efficacy of antihelminthic compound; Clorsulon against experimental *Schistosoma mansoni* infection. J. Egypt. Soc. Parasitol. 37, 171–188.

Murray, C.J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A.D., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J.A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S.Y., Ali, M.K., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Bahalim, A.N., Barker-Collo, S., Barrero, L.H., Bartels, D.H., Basanez, M.G., Baxter, A., Bell, M.L., Benjamin, E.J., Bennett, D., Bernabe, E., Bhalla, K., Bhandari, B., Bikbov, B., Bin Abdulhak, A., Birbeck, G., Black, J.A., Blencowe, H., Blore, J.D., Blyth, F., Bolliger, I., Bonaventure, A., Boufous, S., Bourne, R., Boussinesq, M., Braithwaite, T., Brayne, C., Bridgett, L., Brooker, S., Brooks, P., Brugha, T.S., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Buckle, G., Budke, C.M., Burch, M., Burney, P., Burstein, R., Calabria, B., Campbell, B., Canter, C.E., Carabin, H., Carapetis, J., Carmona, L., Cella, C., Charlson, F., Chen, H., Cheng, A.T., Chou, D., Chugh, S.S., Coffeng, L.E., Colan, S.D., Colquhoun, S., Colson, K.E., Condon, J., Connor, M.D., Cooper, L.T., Corriere, M., Cortinovis, M., de Vaccaro, K.C., Couser, W., Cowie, B.C., Criqui, M.H., Cross, M., Dabhadkar, K.C., Dahiya, M., Dahodwala, N., Damsere-Derry, J., Danaei, G., Davis, A., De Leo, D., Degenhardt, L., Dellavalle, R., Delossantos, A., Denenberg, J., Derrett, S., Des Jarlais, D.C., Dharmaratne, S.D., Dherani, M., Diaz-Torne, C., Dolk, H., Dorsey, E.R., Driscoll, T., Duber, H., Ebel, B., Edmond, K., Elbaz, A., Ali, S.E., Erskine, H., Erwin, P.J., Espindola, P., Ewoigbokhan, S.E., Farzadfar, F., Feigin, V., Felson, D.T., Ferrari, A., Ferri, C.P., Fevre, E.M., Finucane, M.M., Flaxman, S., Flood, L., Foreman, K., Forouzanfar, M.H., Fowkes, F.G., Fransen, M., Freeman, M.K., Gabbe, B.J., Gabriel, S.E., Gakidou, E., Ganatra, H.A., Garcia, B., Gaspari, F., Gillum, R.F., Gmel, G., Gonzalez-Medina, D., Gosselin, R., Grainger, R., Grant, B., Groeger, J., Guillemin, F., Gunnell, D., Gupta, R., Haagsma, J., Hagan, H., Halasa, Y.A., Hall, W., Haring, D., Haro, J.M., Harrison, J.E., Havmoeller, R., Hay, R.J., Higashi, H., Hill, C., Hoen, B., Hoffman, H., Hotez, P.J., Hoy, D., Huang, J.J., Ibeanusi, S.E., Jacobsen,

K.H., James, S.L., Jarvis, D., Jasrasaria, R., Jayaraman, S., Johns, N., Jonas, J.B., Karthikeyan, G., Kassebaum, N., Kawakami, N., Keren, A., Khoo, J.P., King, C.H., Knowlton, L.M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Laden, F., Lalloo, R., Laslett, L.L., Lathlean, T., Leasher, J.L., Lee, Y.Y., Leigh, J., Levinson, D., Lim, S.S., Limb, E., Lin, J.K., Lipnick, M., Lipshultz, S.E., Liu, W., Loane, M., Ohno, S.L., Lyons, R., Mabweijano, J., MacIntyre, M.F., Malekzadeh, R., Mallinger, L., Manivannan, S., Marcenes, W., March, L., Margolis, D.J., Marks, G.B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B.M., McAnulty, J.H., McDermott, M.M., McGill, N., McGrath, J., Medina-Mora, M.E., Meltzer, M., Mensah, G.A., Merriman, T.R., Meyer, A.C., Miglioli, V., Miller, M., Miller, T.R., Mitchell, P.B., Mock, C., Mocumbi, A.O., Moffitt, T.E., Mokdad, A.A., Monasta, L., Montico, M., Moradi-Lakeh, M., Moran, A., Morawska, L., Mori, R., Murdoch, M.E., Mwaniki, M.K., Naidoo, K., Nair, M.N., Naldi, L., Narayan, K.M., Nelson, P.K., Nelson, R.G., Nevitt, M.C., Newton, C.R., Nolte, S., Norman, P., Norman, R., O'Donnell, M., O'Hanlon, S., Olives, C., Omer, S.B., Ortblad, K., Osborne, R., Ozgediz, D., Page, A., Pahari, B., Pandian, J.D., Rivero, A.P., Patten, S.B., Pearce, N., Padilla, R.P., Perez-Ruiz, F., Perico, N., Pesudovs, K., Phillips, D., Phillips, M.R., Pierce, K., Pion, S., Polanczyk, G.V., Polinder, S., Pope 3rd, C.A., Popova, S., Porrini, E., Pourmalek, F., Prince, M., Pullan, R.L., Ramaiah, K.D., Ranganathan, D., Razavi, H., Regan, M., Rehm, J.T., Rein, D.B., Remuzzi, G., Richardson, K., Rivara, F.P., Roberts, T., Robinson, C., De Leon, F.R., Ronfani, L., Room, R., Rosenfeld, L.C., Rushton, L., Sacco, R.L., Saha, S., Sampson, U., Sanchez-Riera, L., Sanman, E., Schwebel, D.C., Scott, J.G., Segui-Gomez, M., Shahraz, S., Shepard, D.S., Shin, H., Shivakoti, R., Singh, D., Singh, G.M., Singh, J.A., Singleton, J., Sleet, D.A., Sliwa, K., Smith, E., Smith, J.L., Stapelberg, N.J., Steer, A., Steiner, T., Stolk, W.A., Stovner, L.J., Sudfeld, C., Syed, S., Tamburlini, G., Tavakkoli, M., Taylor, H.R., Taylor, J.A., Taylor, W.J., Thomas, B., Thomson, W.M., Thurston, G.D., Tleyjeh, I.M., Tonelli, M., Towbin, J.A., Truelsen, T., Tsilimbaris, M.K., Ubeda, C., Undurraga, E.A., van der Werf, M.J., van Os, J., Vavilala, M.S., Venketasubramanian, N., Wang, M., Wang, W., Watt, K., Weatherall, D.J., Weinstock, M.A., Weintraub, R., Weisskopf, M.G., Weissman, M.M., White, R.A., Whiteford, H., Wiebe, N., Wiersma, S.T., Wilkinson, J.D., Williams, H.C., Williams, S.R., Witt, E., Wolfe, F., Woolf, A.D., Wulf, S., Yeh, P.H., Zaidi, A.K., Zheng, Z.J., Zonies, D., Lopez, A.D., 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380, 2197–2223.

Musgrave, I.A., Hawes, R.B., Jameson, J.L., Sloane, R.A., Quayle, P.A., 1979. Mebendazole – evaluation of a new antihelminthic for trichuriasis, hookworm, and strongyloidiasis. Med. J. Aust. 1, 403–405.

Nfon, C.K., Makepeace, B.L., Njongmeta, L.M., Tanya, V.N., Trees, A.J., 2007. Lack of resistance after re-exposure of cattle cured of *Onchocerca ochengi* infection with oxytetracycline. Am. J. Trop. Med. Hyg. 76, 67–72.

N'Goran, E.K., Utzinger, J., Gnaka, H.N., Yapi, A., N'Guessan, N.A., Kigbafori, S.D., Lengeler, C., Chollet, J., Shuhua, X., Tanner, M., 2003. Randomized double-blind, placebo-controlled trial of oral artemether for the prevention of patent *Schistosoma haematobium* infections. Am. J. Trop. Med. Hyg. 68, 24–32.

O'Connor, K.A., Roth, B.L., 2005. Finding new tricks for old drugs: an efficient route for public-sector drug discovery. Nat. Rev. Drug Dis. 4, 1005–1014.

Olliaro, P., Seiler, J., Kuesel, A., Horton, J., Clark, J.N., Don, R., Keiser, J., 2011. Potential drug development candidates for human soil-transmitted helminthiases. PLoS Negl. Trop. Dis. 5, e1138.

Ortiz, P., Terrones, S., Cabrera, M., Hoban, C., Ceballos, L., Moreno, L., Canton, C., Donadeu, M., Lanusse, C., Alvarez, L., 2014. Oxfendazole flukicidal activity in pigs. Acta Trop. 136, 10–13.

Padhy, B.M., Gupta, Y.K., 2011. Drug repositioning: re-investigating existing drugs for new therapeutic indications. J. Postgrad. Med. 57, 153–160.

Pawłowski, Z.S., Vuitton, D.A., Ammann, R.W., Kern, P., Craig, P.S., Dar, K.F., De Rosa, F., Filice, C., Gottstein, B., Grimm, F., Macpherson, C.N.L., Sato, N., Todorov, T., Uchino, J., von Sinner, W., Wen, H., 2001. Echinococcosis in humans: clinical aspects, diagnosis and treatment. In: Eckert, J., Gemmell, M., Meslin, F.-X., Pawlowski, Z., (Eds.), WHO/OIE Manual on Echinococcosis in Humans and Animals: a Public Health Problem of Global Concern World Organisation for Animal Health and World Health Organization, Paris, pp. 20–71.

Pearson, R.D., Hewlett, E.L., 1985. Niclosamide therapy for tapeworm infections. Ann. Intern. Med. 102, 550–551.

Pedrique, B., Strub-Wourgaft, N., Some, C., Olliaro, P., Trouiller, P., Ford, N., Pécoul, B., Bradol, J.-H., 2013. The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment. The Lancet Global Health 1, e371–e379.

Perez-Molina, J.A., Diaz-Menendez, M., Gallego, J.I., Norman, F., Monge-Maillo, B., Ayala, A.P., Lopez-Velez, R., 2011. Evaluation of nitazoxanide for the treatment of disseminated cystic echinococcosis: report of five cases and literature review. Am. J. Trop. Med. Hyg. 84, 351–356.

Perez del Villar, L., Burguillo, F.J., Lopez-Aban, J., Muro, A., 2012. Systematic review and meta-analysis of artemisinin based therapies for the treatment and prevention of schistosomiasis. PLoS One 7, e45867.

Qian, M.B., Yap, P., Yang, Y.C., Liang, H., Jiang, Z.H., Li, W., Tan, Y.G., Zhou, H., Utzinger, J., Zhou, X.N., Keiser, J., 2013. Efficacy and safety of tribendimidine against *Clonorchis sinensis*. Clin. Infect. Dis. 56, e76–82.

Ranjan, S., DeLay, R., 2004. Therapeutic and persistent efficacy of moxidectin 1% nonaqueous injectable formulation against natural and experimentally induced lung and gastrointestinal nematodes in cattle. Vet. Parasitol. 120, 305–317.

Rao, R.U., Huang, Y., Fischer, K., Fischer, P.U., Weil, G.J., 2009. *Brugia malayi*: effects of nitazoxanide and tizoxanide on adult worms and microfilariae of filarial nematodes. Exp. Parasitol. 121, 38–45.

Reichard, M.V., Wolf, R.F., Carey, D.W., Garrett, J.J., Briscoe, H.A., 2007. Efficacy of fenbendazole and milbemycin oxime for treating baboons (*Papio cynocephalus anubis*) infected with *Trichuris trichiura*. J. Am. Assoc. Lab. Anim. Sci. 46, 42–45.

Reinemeyer, C.R., Cleale, R.M., 2002. Dose confirmation studies of moxidectin 1% non-aqueous injectable and moxidectin 0.5% pour-on formulations against experimentally induced infections of larval and adult stage *Oesophagostomum radiatum* and *Trichuris discolor* in cattle. Vet. Parasitol. 108, 75–83.

Reuter, S., Buck, A., Grebe, O., Nussle-Kugele, K., Kern, P., Manfras, B.J., 2003a. Salvage treatment with amphotericin B in progressive human alveolar echinococcosis. Antimicrob. Agents Chemother. 47, 3586–3591.

Reuter, S., Merkle, M., Brehm, K., Kern, P., Manfras, B., 2003b. Effect of amphotericin B on larval growth of *Echinococcus multilocularis*. Antimicrob. Agents Chemother. 47, 620–625.

Reuter, S., Manfras, B., Merkle, M., Harter, G., Kern, P., 2006. *In vitro* activities of itraconazole, methiazole, and nitazoxanide versus *Echinococcus multilocularis* larvae. Antimicrob. Agents Chemother. 50, 2966–2970.

Richards Jr., F.O., Amann, J., Arana, B., Punkosdy, G., Klein, R., Blanco, C., Lopez, B., Mendoza, C., Dominguez, A., Guarner, J., Maguire, J.H., Eberhard, M., 2007. No depletion of Wolbachia from *Onchocerca volvulus* after a short course of rifampin and/or azithromycin. Am. J. Trop. Med. Hyg. 77, 878–882.

Richter, D., Richter, J., Gruner, B., Kranz, K., Franz, J., Kern, P., 2013. *In vitro* efficacy of triclabendazole and clorsulon against the larval stage of *Echinococcus multilocularis*. Parasitol. Res. 112, 1655–1660.

Rim, H.J., Lee, J.S., Joo, K.H., Kim, Y.S., 1981. Anthelmintic effects of single doses of fenbendazole and oxantel-pyrantel pamoate to the intestinal nematodes. Korean J. Parasitol. 19, 95–100.

Romero Cabello, R., Guerrero, L.R., Munoz Garcia, M.R., Geyne Cruz, A., 1997. Nitazoxanide for the treatment of intestinal protozoan and helminthic infections in Mexico. Trans. R. Soc. Trop. Med. Hyg. 91, 701–703.

Rossignol, J.F., 2009. Thiazolides: a new class of antiviral drugs. Expert Opin. Drug Metab. Toxicol. 5, 667–674.

Rossignol, J.F., Maisonneuve, H., 1984. Nitazoxanide in the treatment of *Taenia saginata* and *Hymenolepis nana* infections. Am. J. Trop. Med. Hyg. 33, 511–512.

Saeki, H., Ishii, T., Ohta, M., Tsuchiya, S., Furuya, T., Fujii, T., 1995. Evaluation of anthelmintic efficacy of doramectin against gastrointestinal nematodes by fecal examination in cattle in Japan. J. Vet. Med. Sci. 57, 1057–1061.

Salem, H.H., el-Allaf, G., 1969. Treatment of *Taenia saginata* and *Hymenolepis nana* infections with paromomycin. Trans. R. Soc. Trop. Med. Hyg. 63, 833–836.

Sanchez-Carrillo, M.C., Beltran-Hernandez, F., 1977. Therapeutic effectiveness of fenbendazole (HOE-881) in helminthiasis transmitted by the soil in the state of Chiapas, Mexico. Salud Publica Mex. 19, 691–700.

Schad, G.A., 1986. Cyclosporine may eliminate the threat of overwhelming strongyloidiasis in immunosuppressed patients. J. Infect. Dis. 153, 178.

Sekhon, B.S., 2013. Repositioning drugs and biologics: Retargeting old/existing drugs for potential new therapeutic applications. J. Pharm. Educ. Res. 4, 1–15.

Shikiya, K., Kuniyoshi, T., Higashionna, A., Arakkaki, T., Oyakawa, T., Kadena, K., Kinjo, F., Saito, A., Asato, R., 1990. Treatment of strongyloidiasis with mebendazole and its combination with thiabendazole. Kansenshogaku zasshi. J. Jpn. Assoc. Infect. Dis. 64, 1408–1415.

Shikiya, K., Kinjo, N., Ikema, M., Yamashiro, A., Uechi, H., Oyakawa, T., Kinjo, F., Saito, A., Nakamura, H., Ohwan, T., et al., 1991. Comparison of efficacy of powder and tablet of mebendazole in the treatment of strongyloidiasis. Kansenshogaku zasshi. J. Jpn. Assoc. Infect. Dis. 65, 681–686.

Soo, G.W., Law, J.H., Kan, E., Tan, S.Y., Lim, W.Y., Chay, G., Bukhari, N.I., Segarra, I., 2010. Differential effects of ketoconazole and primaquine on the pharmacokinetics and tissue distribution of imatinib in mice. Anticancer Drugs 7, 695–703.

Sotelo, J., Escobedo, F., Penagos, P., 1988. Albendazole vs praziquantel for therapy for neurocysticercosis. A controlled trial. Arch. Neurol. 45, 532–534.

Sotelo, J., del Brutto, O.H., Penagos, P., Escobedo, F., Torres, B., Rodriguez-Carbajal, J., Rubio-Donnadieu, F., 1990. Comparison of therapeutic regimen of anticysticercal drugs for parenchymal brain cysticercosis. J. Neurol. 237, 69–72.

Soukhathammavong, P., Odermatt, P., Sayasone, S., Vonghachack, Y., Vounatsou, P., Hatz, C., Akkhavong, K., Keiser, J., 2011. Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, tribendimidine, and praziquantel in patients with *Opisthorchis viverrini*: a randomised, exploratory, open-label, phase 2 trial. Lancet Infect. Dis. 11, 110–118.

Specht, S., Mand, S., Marfo-Debrekyei, Y., Debrah, A.Y., Konadu, P., Adjei, O., Buttner, D.W., Hoerauf, A., 2008. Efficacy of 2- and 4-week rifampicin treatment on the Wolbachia of *Onchocerca volvulus*. Parasitol. Res. 103, 1303–1309.

Speich, B., Ame, S.M., Ali, S.M., Alles, R., Hattendorf, J., Utzinger, J.R., Albonico, M., Keiser, J., 2012. Efficacy and safety of nitazoxanide, albendazole, and nitazoxanide-albendazole against *Trichuris trichiura* infection: a randomized controlled trial. PLoS Negl. Trop. Dis. 6, e1685.

Speich, B., Marti, H., Ame, S.M., Ali, S.M., Bogoch, I.I., Utzinger, J., Albonico, M., Keiser, J., 2013. Prevalence of intestinal protozoa infection among school-aged children on Pemba Island, Tanzania, and effect of single-dose albendazole, nitazoxanide and albendazole-nitazoxanide. Parasite Vectors 6, 3.

Speich, B., Ame, S.M., Ali, S.M., Alles, R., Huwyler, J., Hattendorf, J., Utzinger, J., Albonico, M., Keiser, J., 2014. Oxantel pamoate-albendazole for *Trichuris trichiura* infection. New Engl. J. Med. 370, 610–620.

Spicher, M., Roethlisberger, C., Lany, C., Stadelmann, B., Keiser, J., Ortega-Mora, L.M., Gottstein, B., Hemphill, A., 2008. *In vitro* and *in vivo* treatments of echinococcus protoscoleces and metacestodes with artemisinin and artemisinin derivatives. Antimicrob. Agents Chemother. 52, 3447–3450.

Steinmann, P., Zhou, X.N., Du, Z.W., Jiang, J.Y., Xiao, S.H., Wu, Z.X., Zhou, H., Utzinger, J., 2008. Tribendimidine and albendazole for treating soil-transmitted

helminths, Strongyloides stercoralis and *Taenia* spp.: open-label randomized trial. PLoS Negl. Trop. Dis. 2, e322.
Stettler, M., Fink, R., Walker, M., Gottstein, B., Geary, T.G., Rossignol, J.F., Hemphill, A., 2003. *In vitro* parasiticidal effect of nitazoxanide against *Echinococcus multilocularis* metacestodes. Antimicrob. Agents Chemother. 47, 467–474.
Stettler, M., Rossignol, J.F., Fink, R., Walker, M., Gottstein, B., Merli, M., Theurillat, R., Thormann, W., Dricot, E., Segers, R., Hemphill, A., 2004. Secondary and primary murine alveolar echinococcosis: combined albendazole/nitazoxanide chemotherapy exhibits profound anti-parasitic activity. Int. J. Parasitol. 34, 615–624.
Stewart, T.B., Fox, M.C., Wiles, S.E., 1996. Doramectin efficacy against gastrointestinal nematodes in pigs. Vet. Parasitol. 66, 101–108.
Stewart, T.B., Wiles, S.E., Miller, J.E., Rulli, R.D., 1999. Efficacy of moxidectin 0.5% pour-on against swine nematodes. Vet. Parasitol. 87, 39–44.
Stothard, J.R., Sousa-Figueiredo, J.C., Betson, M., Bustinduy, A., Reinhard-Rupp, J., 2013. Schistosomiasis in African infants and preschool children: let them now be treated! Trends Parasitol. 29, 197–205.
Supali, T., Djuardi, Y., Pfarr, K.M., Wibowo, H., Taylor, M.J., Hoerauf, A., Houwing-Duistermaat, J.J., Yazdanbakhsh, M., Sartono, E., 2008. Doxycycline treatment of *Brugia malayi*-infected persons reduces microfilaremia and adverse reactions after diethylcarbamazine and albendazole treatment. Clin. Infect. Dis. 46, 1385–1393.
Takayanagui, O.M., Jardim, E., 1992. Therapy for neurocysticercosis. Comparison between albendazole and praziquantel. Arch. Neurol. 49, 290–294.
Taylor, M.J., Makunde, W.H., McGarry, H.F., Turner, J.D., Mand, S., Hoerauf, A., 2005. Macrofilaricidal activity after doxycycline treatment of *Wuchereria bancrofti*: a double-blind, randomised placebo-controlled trial. Lancet 365, 2116–2121.
Taylor, M.J., Awadzi, K., Basanez, M.G., Biritwum, N., Boakye, D., Boatin, B., Bockarie, M., Churcher, T.S., Debrah, A., Edwards, G., Hoerauf, A., Mand, S., Matthews, G., Osei-Atweneboana, M., Prichard, R.K., Wanji, S., Adjei, O., 2009. Onchocerciasis control: vision for the future from a Ghanian perspective. Parasit. Vectors 2, 7.
Terrazas, L.I., Bojalil, R., Govezensky, T., Larralde, C., 1994. A role for 17-beta-estradiol in immunoendocrine regulation of murine cysticercosis (Taenia crassiceps). J. Parasitol. 80, 563–568.
Toh, S.Q., Glanfield, A., Gobert, G.N., Jones, M.K., 2010. Heme and blood-feeding parasites: friends or foes? Parasit. Vectors 3, 108.
Topcu, O., Sumer, Z., Tuncer, E., Aydin, C., Koyuncu, A., 2009. Efficacy of chlorhexidine gluconate during surgery for hydatid cyst. World J. Surg. 33, 1274–1280.
Tritten, L., Silbereisen, A., Keiser, J., 2012. Nitazoxanide: *In vitro* and *in vivo* drug effects against *Trichuris muris* and *Ancylostoma ceylanicum*, alone or in combination. Int. J. Parasitol. Drugs Drug Resist. 2, 98–105.
Tschen, E.H., Tschen, E.A., Smith, E.B., 1981. Cutaneous cysticercosis treated with metrifonate. Arch. Dermatol. 117, 507–509.
Tu, Y., 2011. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nat. Med. 17, 1217–1220.
Turner, J.D., Mand, S., Debrah, A.Y., Muehlfeld, J., Pfarr, K., McGarry, H.F., Adjei, O., Taylor, M.J., Hoerauf, A., 2006. A randomized, double-blind clinical trial of a 3-week course of doxycycline plus albendazole and ivermectin for the treatment of *Wuchereria bancrofti* infection. Clin. Infect. Dis. 42, 1081–1089.
Turner, J.D., Tendongfor, N., Esum, M., Johnston, K.L., Langley, R.S., Ford, L., Faragher, B., Specht, S., Mand, S., Hoerauf, A., Enyong, P., Wanji, S., Taylor, M.J., 2010. Macrofilaricidal activity after doxycycline only treatment of *Onchocerca volvulus* in an area of *Loa loa* co-endemicity: a randomized controlled trial. World J. Surg. 4, e660.
Utzinger, J., N'Goran, E.K., N'Dri, A., Lengeler, C., Xiao, S., Tanner, M., 2000. Oral artemether for prevention of *Schistosoma mansoni* infection: randomised controlled trial. Lancet 355, 1320–1325.
Utzinger, J., Keiser, J., 2004. Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control. Expert Opin. Pharmacother. 5, 263–285.
Utzinger, J., Xiao, S.H., Tanner, M., Keiser, J., 2007. Artemisinins for schistosomiasis and beyond. Curr. Opin. Investig. Drugs 8, 105–116.
Utzinger, J., Tanner, M., Keiser, J., 2010. ACTs for schistosomiasis: do they act? Lancet Infect. Dis. 10, 579–581.
van Blitterswijk, W.J., Verheij, M., 2013. Anticancer mechanisms and clinical application of alkylphospholipids. Biochim. Biophys. Acta 1831, 663–674.
Van Kerckhoven, I., Kumar, V., 1988. Macrofilaricidal activity of oral flubendazole on *Brugia pahangi*. Trans. R. Soc. Trop. Med. Hyg. 82, 890–891.
Vargas-Villavicencio, J.A., Larralde, C., De Leon-Nava, M.A., Escobedo, G., Morales-Montor, J., 2007. Tamoxifen treatment induces protection in murine cysticercosis. J. Parasitol. 93, 1512–1517.
Vermund, S.H., MacLeod, S., Goldstein, R.G., 1986. Taeniasis unresponsive to a single dose of niclosamide: case report of persistent infection with *Taenia saginata* and a review of therapy. Rev. Infect. Dis. 8, 423–426.
von Samson-Himmelstjerna, G., Harder, A., Sangster, N.C., Coles, G.C., 2005. Efficacy of two cyclooctadepsipeptides, PF1022A and emodepside, against anthelmintic-resistant nematodes in sheep and cattle. Parasitology 130, 343–347.
Walker, M., Rossignol, J.F., Torgerson, P., Hemphill, A., 2004. *In vitro* effects of nitazoxanide on *Echinococcus granulosus* protoscoleces and metacestodes. J. Antimicrob. Chemother. 54, 609–616.
Wang, X., Zhao, Q., Vargas, M., Dong, Y., Sriraghavan, K., Keiser, J., Vennerstrom, J.L., 2011. The activity of dispiro peroxides against *Fasciola hepatica*. Bioorg. Med. Chem. Lett. 21, 5320–5323.
Wanji, S., Tendongfor, N., Nji, T., Esum, M., Che, J.N., Nkwescheu, A., Alassa, F., Kamnang, G., Enyong, P.A., Taylor, M.J., Hoerauf, A., Taylor, D.W., 2009. Community-directed delivery of doxycycline for the treatment of onchocerciasis in areas of co-endemicity with loiasis in Cameroon. Parasit. Vectors 2, 39.
Wells, T.N., 2013. Discovering and developing new medicines for malaria control and elimination. Infect. Disord. Drug Targets 13, 292–302.
WHO, 1996. Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. Bull. World Health Organ. 74, 231–242.
WHO, 2006. Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers. World Health Organization, Geneva.
WHO, 2011. Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation WHO, Geneva, pp. 1–42.
WHO, 2013. WHO model list on essential medicines. World Health Organization, Geneva.
WHO/FAO/OIE, 2005. WHO/FAO/OIE Guidelines for the surveillance, prevention and control of taeniosis/cysticercosis, Paris World Organisation for Animal Health.
Wimmersberger, D., Tritten, L., Keiser, J., 2013. Development of an *in vitro* drug sensitivity assay for *Trichuris muris* first-stage larvae. Parasit. Vectors 6, 42.
Xiao, S.H., Keiser, J., Chollet, J., Utzinger, J., Dong, Y., Vennerstrom, J.L., Tanner, M., 2007. The *in vitro* and *in vivo* activities of synthetic trioxolanes on major human schistosome species. Antimicrob. Agents Chemother. 51, 1440–1445.
Xiao, S.H., Xue, J., Xu, L.L., Zheng, Q., Qiang, H.Q., Zhang, Y.N., 2009. The *in vitro* and *in vivo* effect of tribendimidine and its metabolites against *Clonorchis sinensis*. Parasitol. Res. 105, 1497–1507.
Xiao, S.H., Xue, J., Li-li, X., Zhang, Y.N., Qiang, H.Q., 2010. Effectiveness of mefloquine against *Clonorchis sinensis* in rats and *Paragonimus westermani* in dogs. Parasitol. Res. 107, 1391–1397.
Xiao, S.H., Mei, J.Y., Jiao, P.Y., 2011. *Schistosoma japonicum*-infected hamsters (*Mesocricetus auratus*) used as a model in experimental chemotherapy with praziquantel, artemether, and OZ compounds. Parasitol. Res. 108, 431–437.
Xiao, S.H., Xue, J., Mei, J.Y., Jiao, P.Y., 2012. Effectiveness of synthetic trioxolane OZ78 against *Schistosoma japonicum* in mice and rabbits. Parasitol. Res. 110, 2307–2314.
Xiao, S.H., Utzinger, J., Tanner, M., Keiser, J., Xue, J., 2013. Advances with the Chinese anthelminthic drug tribendimidine in clinical trials and laboratory investigations. Acta Trop. 126, 115–126.
Xue, J., Wang, X., Dong, Y., Vennerstrom, J.L., Xiao, S.H., 2014. Effect of ozonide OZ418 against *Schistosoma japonicum* harbored in mice. Parasitol. Res. Epub ahead of print.
Yakoot, M., 2010. A short review of the anthelmintic role of Mirazid. Arq. Gastroenterol. 47, 393–394.
Yangco, B.G., Klein, T.W., Deresinski, S.C., Vickery, A.C., Craig, C.P., 1981. Flubendazole and mebendazole in the treatment of trichuriasis and other helminthiases. Clin. Ther. 4, 285–290.
Yawzinski, T.A., Tucker, C., Featherson, H., Johnson, Z., Wood-Huels, N., 1997. Endectocidal efficacies of doramectin in naturally parasitized pigs. Vet. Parasitol. 70, 123–128.
Yuan, G., Xu, J., Qu, T., Wang, B., Zhang, R., Wei, C., Guo, R., 2010. Metabolism and disposition of tribendimidine and its metabolites in healthy Chinese volunteers. Drugs R D 10, 83–90.
Zaha, O., Hirata, T., Kinjo, F., Saito, A., 2000. Strongyloidiasis–progress in diagnosis and treatment. Internal medicine (Tokyo, Japan) 39, 695–700.
Zahner, H., Taubert, A., Harder, A., von Samson-Himmelstjerna, G., 2001. Filaricidal efficacy of anthelmintically active cyclodepsipeptides. Int. J. Parasitol. 31, 1515–1522.
Zhao, Q., Vargas, M., Dong, Y., Zhou, L., Wang, X., Sriraghavan, K., Keiser, J., Vennerstrom, J.L., 2010. Structure-activity relationship of an ozonide carboxylic acid (OZ78) against *Fasciola hepatica*. J. Med. Chem. 53, 4223–4233.
Zumaquero-Rios, J.L., Sarracent-Perez, J., Rojas-Garcia, R., Rojas-Rivero, L., Martinez-Tovilla, Y., Valero, M.A., Mas-Coma, S., 2013. Fascioliasis and intestinal parasitoses affecting schoolchildren in Atlixco, Puebla State, Mexico: epidemiology and treatment with nitazoxanide. PLoS Negl. Trop. Dis. 7, e2553.
Zumla, A., Keiser, J., 2012. Preface: tropical diseases. Infect. Dis. Clin. North Am. 26, xv–xvii.