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Preventive chemotherapy and anthelmintic resistance of soil-transmitted helminths – Can we learn nothing from veterinary medicine?

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A B S T R A C T

Current parasite control programs in veterinary species have moved away from mass anthelmintic treatment approaches due to the emergence of significant anthelmintic resistance (AR), and the availability of few classes of anthelmintics. A number of parallels between livestock and human helminths exist that warn of the risk of AR in human soil-transmitted helminthiases, yet current public health interventions continue to prioritize mass treatment strategies, a known risk factor for AR. This review discusses the existing parallels between human and animal helminth biology and management, along with current public health recommendations and strategies for helminth control in humans. The effectiveness of current recommendations and alternative management strategies are considered.

1. Introduction

Warnings issued in a review 25 years ago [1] stated that those responsible for the control of human helminths needed to learn from the challenges veterinarians and parasitologists have experienced with managing gastrointestinal nematodes (GIN) in farm animals. Several years later the same authors [2] went on to say that the biological, epidemiological, and pharmaceutical similarities between human and livestock helminths are so great that “optimism (as regards the development of AR in human helminths) may amount to complacent neglect.” They spoke of the danger of producing resistant helminths through mass therapy programs while simultaneously urging careful monitoring for any signs of the development of AR [1–3]. Geerts and Gryseels [2] also made the distinction that the AR problem in livestock has had economic ramifications and while this alone is devastating, widespread AR in humans would be considered a “serious public health problem” that would likely result in increased morbidity and mortality from human helminths [2]. Current parasite control programs in small ruminants [4–6] and horses [7] have moved away from “blanket” or mass treatment approaches to parasite control to a more integrated approach due to the emergence of significant AR in these species [8–10].

Risk factors for AR development include: parasite biology and epidemiology, the dynamics of the host–parasite relationship, treatment frequency, treatment strategies that result in various levels of refugia and differences in anthelmintic pharmacokinetics between host species [9]. Preserving “refugia” (the proportion of populations of parasites not exposed to anthelmintics) is the current goal of parasite control in small ruminants [5] and horses [7,8] and has been deemed the single most important factor involved in the selection of AR parasites [9]. A selective approach to deworming is currently recommended in veterinary medicine in order to preserve refugia and slow AR. Animals in the herd that are the least clinically affected based on fecal egg counts (FEC) and/or FAMACHA© scoring are left untreated. Anthelmintics are then administered to the most affected when there are more eggs and larvae on the pasture so the presence of susceptible parasite populations on pasture will “dilute” the resistant populations and thereby preserve refugia. FAMACHA© is an on-farm test used to evaluate small ruminants for the load of *Haemonchus contortus*, or barberpole worm, a blood-sucking nematode, based on lower eyelid color as color correlates with anemia [6].

A broad mass-treatment approach, referred to as preventive chemotherapy, continues to be the cornerstone of human helminth control [12] despite its reported ineffectiveness [13–16]. Currently, large scale mass treatment campaigns take place in certain low-middle income countries with school children and women of child-bearing age as the primary targets. In these systems, there is no standardized surveillance protocol for AR [17]. As we have painfully learned in veterinary medicine, once AR has occurred in livestock GIN, full reversion to susceptibility is never observed [18]. There is much to be learned from

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veterinary medicine and the pitfalls that veterinary parasitologists, veterinarians and animal owners/producers have navigated after years of mass, unregulated anthelmintic treatment in animal species.

1.1. Soil-transmitted helminths in humans

There are three major human major soil-transmitted helminths (STHs), *Ascaris lumbricoides* (roundworm), *Necator americanus/ Ancylostoma duodenale*, *Ancylostoma ceylanicum* (the hookworms) and *Trichuris trichiura* (whipworm). These are among the most prevalent parasites worldwide [19,20]. One and a half billion people are estimated as being infected by STHs [12]. In 2015, the global burden of infections with STHs was estimated at 3.4 million disability adjusted life years [21]. Significant morbidity is observed in hundreds of millions of people due to their infection, with children displaying the greatest morbidity when infected. Infected pregnant women reportedly also suffer significant morbidity, and hookworm-associated anemia is thought to contribute to maternal mortality [19]. Approximately 135,000 deaths occur annually, primarily due to hookworm infections and subsequent anemia, intestinal or biliary obstruction [22] due to roundworm infections and chronic dysentery from whipworm infections [23]. Most affected countries are in low-middle income regions in Asia, Sub-Saharan Africa, and Latin America, and many of the illnesses resulting from these parasites have been classified by the WHO as neglected tropical diseases or NTDs [12]. This “neglect” has been attributed to a relatively low mortality from NTDs as compared to HIV/AIDS, malaria and tuberculosis, which historically have formed the primary focus of the global public health agenda. Inadequate water supply and sanitation, crowded living conditions along with lack of access to health care and low levels of education make poorer people more susceptible to infection and disease [24], while the study of STHs is allotted less than 1% of global health research dollars [25,26].

Specific risk factors for human STH infection have been identified and include: poverty, lack of sanitation, inadequate hygiene such as absence of hand-washing with soap before eating and after defecation, and walking barefoot [27]. Multi-species STH infections are common among those infected. Transmission of STHs is primarily through contact with contaminated soil in the case of hookworms, and via consumption of egg-contaminated foods in the case of ascariasis and trichuriasis [27]. The distribution of the intensity of infection (traditionally measured as eggs per gram of feces) is variable, with most patients harboring infections of lower intensity and few individuals with heavy infection [27]. Most studies suggest that approximately 70% of the worm population is hosted by 15% of the host population [24], similar to the “80:20 rule” of livestock parasite infection, a term referred to by parasitologists as “over-dispersion” [6]. The most intense infections of *A. lumbricoides* and *T. trichiura* are found in children 5 to 15 years old, with a decline in intensity and frequency seen in adults. According to the literature, it is unclear if this decline is due to acquired immunity, decreased exposure or a combination of these two factors. In veterinary species, young animals and pregnant females are similarly the high-risk groups for parasite infection and are typically more intensely affected [28]. The susceptibility of young animals is a consequence of an inability to develop an effective acquired immune response, and in the peri-parturient female, susceptibility arises from a temporary loss of acquired immunity [28]. In contrast, heavy hookworm infections remain high in human adults, and even in the elderly. Affected children experience malnutrition, stunted growth, as well as impaired cognitive and learning abilities. The small number of individuals with heavy infections are at a greater risk of disease, are likely the most in need of treatment, and are also the main source of environmental contamination [24]. Identification and effective treatment of these individuals is essential in order to establish a successful targeted, selective chemotherapy program and to slow the development of anthelmintic resistance.

1.2. Current public health interventions and short-comings

The United Nation's General Assembly adopted access to water and sanitation as a basic human right, and one of the UN Sustainable Development Goals for 2030 is to ensure access to water and sanitation for all [29]. The WHO currently recommends five interventions to control morbidity due to STH infections: preventive chemotherapy; innovative and intensified disease management; vector ecology and management; veterinary public health services; and the provision of safe water, sanitation and hygiene [12]. The organization continues to identify preventive chemotherapy as the primary focus of STH intervention and it “recommends anthelmintic treatment without previous individual diagnosis.” Regular drug treatment of all individuals, regardless of infection status, is the main approach for infection control in areas of heavy infection, and where resources for disease control and funding for sanitation are insufficient [12,25]. Treatment is recommended once yearly if community prevalence exceeds 20%, or twice yearly when community prevalence exceeds 50%, in order to decrease morbidity by reducing the worm burden [12]. By 2020, the WHO (2017) has set a coverage goal of 75% of the 834.7 million preschool and school-aged children that require preventive treatment while no specific target for 2020 has been set for women of reproductive age. Many of the drugs provided in the mass treatment campaigns are donated by pharmaceutical companies and are low-cost generic drugs. This makes mass treatment programs the most cost-effective global public health control measure [30], as well as the most commonly employed intervention. Of the 1556 new drugs marketed between 1975 and 2004, very few drugs were developed to treat the human helminthiases: lymphatic filariasis, onchocerciasis, schistosomiasis and the soil-transmitted helminthiases [29]. There are only six drug options available to combat these infections, which include albendazole, oxamniquine, praziquantel, ivermectin, diethylcarbamazine, and mebendazole. Of these six drugs, two benzimidazoles (albendazole and mebendazole) are most commonly used in mass treatment campaigns for STHs [29], along with levamisole and pyrantel [15]. It is understood by veterinary parasitologists that if AR develops within a class of anthelmintic, all drugs within this class are rendered ineffective [18,31]. If this were to occur in one of the benzimidazoles used against STHs, this would significantly limit treatment options, as there are no new drugs under development [32]. In veterinary medicine there are only four classes of drugs that are available for use against GIN, and they include the benzimidazoles, the pyrimidines, the macrocyclic lactones and the imidazothiazoles. Signs of AR have been found in all drug classes in small ruminants and in three classes in horses, as the imidazothiazoles are not routinely used in this species [9–11,33].

Evidence of the efficacy of mass treatment programs is lacking [13–17,27]. A meta-analysis by Jia et al., [27] showed that after either targeted or mass drug administration, the prevalence of STH infections recovered rapidly in most endemic areas, with the prevalence of all three species found to be at or above half the initial level 6 months post-treatment. At 12 months post-treatment, the prevalence of *A. lumbricoides* and *T. trichiura* had returned to levels close to those before the initial pretreatment. A recent meta-analysis assessed the impact of deworming on children less than 5 years old and pregnant women affected by STHs and found no beneficial effects [14]. While short-term health benefits such as decreased worm burden in treated individuals were found in other studies, the result on overall parasite transmission in the larger community was deemed limited [34]. The variety of prevalence and intensity levels of STH infection in treated populations have been identified as barriers to understanding the effect of anthelmintic treatment [14]. Of great concern are the many studies that provide evidence for decreased anthelmintic efficacy [15,35–39], although there are no documented reports of AR in human helminths to date. However, there has been insufficient AR surveillance [40], which may explain why there are so few reports of decreased efficacy or true AR in the literature. Decreased anthelmintic efficacy, as evidenced by shortened egg reappearance periods, is considered by veterinary parasitologists as the first sign of AR [41]. In veterinary species signs of AR went unobserved until it had already occurred [2], as drug resistance reportedly follows a sigmoidal pattern with a long period of incubation and a few scattered cases followed by the sudden explosion of resistant parasites [42]. Initial resistance allele frequency, treatment frequency, limiting refugia, and under-dosing of anthelmintics have been identified as possibly contributing to the development of AR in livestock and humans [19]. However, little information exists on the frequency of resistant alleles in human STHs, and there appears to be a poor understanding of the exact role that each of the aforementioned factors plays [19]. It has also been shown in veterinary species that AR can be selected for at lower treatment frequencies when the same drug is used repeatedly for many years [2,3] as is the case in STH mass treatment campaigns. Additionally, mathematical models in veterinary parasitology have shown that AR development can be delayed by opting to not treat part of the population and is the basis for targeted-selective deworming in an effort to preserve parasite refugia [43]. Interestingly, more recent studies investigating the current WHO guidelines for STH control are recommending *increases* in mass drug treatment to 75% community-wide and not just school children, no reduction in treatment frequency, and adding *more* anthelmintics to the protocol, particularly in higher-prevalence areas deemed more "resistant to treatment" [44]. Lastly, despite the fact that one of the identified risk factors for AR is under-dosing anthelmintics, mass-treatment programs use lower dosages than recommended in order to reduce cost and side-effects in school-aged children [1,19]. It appears that human mass drug treatment for STHs has a number of risk factors for AR at play. Fortunately, the Bill and Melinda Gates Foundation has recently funded a project called STARWORMS (Stop Anthelmintic Resistant WORMS) aimed at strengthening the surveillance for drug efficacy and AR in STH programs [45]. Veterinary parasitologists say that AR development is inevitable, and all we can hope for is to delay its progress [8] highlighting the need for more holistic, integrated STH interventions.

2. Alternative public health interventions

Sustainable, integrated parasite control is not a novel concept. The Rockefeller Sanitary Commission stated more than 70 years ago: "Cure alone is almost useless in stamping out hookworm disease, because the patient can go out and immediately pick up more hookworms. The cure should be accompanied by a sanitation campaign for the prevention of soil pollution [46]," and several meta-analyses have documented the impact of sanitation on STHs [47–50]. An earlier systematic review and meta-analysis by Fewtrell et al., (2005) [49] looked at the evidence for any change arising from the interventions in diarrheal disease occurrence in non-outbreak conditions and concluded that there was strong consistency in effectiveness of water quality interventions, hygiene interventions (hand, food, water and fomites) and sanitation interventions at reducing diarrheal illness in a wide-range of settings, in many countries, and over many years. Water quality interventions were found to be more effective than previously thought, and multiple interventions were not more effective than single-focused ones, providing evidence that implementation of just one intervention can have significantly positive effects. Ziegelbauer et al., (2012) [47] in a review and meta-analysis, looked specifically at the evidence for sanitation, as defined as access to, and use of, facilities for the safe disposal of human urine and feces, its effects on humans with STHs, and any association with a reduced risk of infection by single or multi-species of STH. They found that the availability and use of sanitation facilities were associated with a reduction in STH-infection prevalence. A systematic review and set of meta-analyses examined evidence of association between STH infection and WASH (water, hygiene and sanitation) [50] concluded that WASH is generally associated with reduced odds of STH infection. The strongest associations in this study were observed between wearing shoes and hookworm infection, the use of piped water and *A. lumbricoides* infection, and treated water and any STH infection. Fifty-four percent lower odds of any STH infection were reported with the use of treated water, piped-water access was associated with reduced odds of *A. lumbricoides* (60%) and *T. trichiura* (43%) infection but there was no association between piped-water access and undifferentiated STHs [50]. WASH interventions consist of a multipronged approach which includes community management of water resources, local and private agency empowerment in order to build capacity to attain safe drinking water, hand hygiene promotion and latrine provision [51]. Several more recent reviews on WASH interventions have shown conflicting results of their impact [51] but this appears to be due to a lack of randomized controlled studies and an overabundance of observational studies [50,52]. Coffeng et al., (2018) [53] have shown, through more rigorous mathematical modeling, a clear added benefit of WASH interventions in preventive chemotherapy programs but that the impact of WASH interventions on STH transmission is highly dependent on worm species, WASH modality, uptake, effectiveness, and pre-control endemicity. Other reasons cited by authors for conflicting evidence include, logistical and ethical difficulties in conducting randomized controlled trials, sufficient time to assess behavioral change, bias, insufficient assessment of compliance to interventions, and insufficient coherence across existing studies such as comparing household-level, school-level, or community level WASH access [54]. Additional recommendations for more rigorous research include: investigation of the quality of WASH infrastructure, such as differences in transmission associated with toilet cleanliness or proper use of infrastructure, the impact of floods and inclement weather on transmission, such as when latrine contents are released across communal areas, and zoonotic infection via contact with animal feces [54].

While it is important to acknowledge that anthelmintic combination therapy improves egg reduction when treating certain STHs [39], the emphasis in human health and the call to arms for new drug development continues to be in the realm of anthelmintic therapy [55] and "repurposing" of anthelmintics [32] rather than looking beyond to more holistic control. If these repurposed therapies merely take the place of the benzimidazoles in preventive chemotherapy programs, AR will inevitably occur in these drug classes as it did in monepantel (Zolvix ®) within less than 2 years after it was introduced for use in sheep in New Zealand [56] or moxidectin use in horses [57]. Sangster (1999) predicted that cyathostomins would develop resistance to moxidectin within 5 years of its introduction into equine parasite control programs, [57] and Trawford et al., confirmed it in 2005 [58]. Some of the targeted-selective deworming strategies in veterinary species include using animal scoring systems such as the FAMACHA© system [6] and the Five Point Check© system of targeted selective treatment [7] to identify GIN-infected small ruminants that are then selected for treatment. Farms or herds where *Haemonchus contortus* is very prevalent can incorporate a number of adjunctive measures for holistic parasite control in order to decrease infective larvae on pastures. Feeding dried forms of anti-parasitic plants in hay or pellets, such as condensed tannin-containing forages, or copper oxide wire particles have been shown to decrease *Haemonchus* egg counts by 67–98% [4,59]. Such measures help the individual animal by decreasing morbidity but also decrease egg shedding and subsequent pasture contamination, which helps the herd. Other alternative therapies that have also been successful utilize the feeding of nematode-trapping fungi (*Duddingtonia flagrans*) to trap and kill infective GIN larvae in feces on pasture [60] as well as vaccines against *H. contortus* in ruminants [4]. Grazing strategies, such as co-grazing with other species who have different grazing behaviors, rotational grazing, tilling or baling larvae into hay, improved nutrition and genetic selection to improve herd or flock parasite resilience and resistance to GIN infection have also been incorporated into the holistic control plan [4]. Research dollars in the fight against human STHs should be directed toward developing promising alternative strategies to anthelmintics for a more holistic, long-term parasite control plan akin to those in veterinary medicine. Does mucous membrane color correlate to level of anemia and hookworm egg counts in humans like the FAMACHA© score does with *Haemonchus contortus* in sheep, goats and camelids? If not, is there another proxy that could be considered? Perhaps recombinant subunit vaccines for STHs, [61] similar to the veterinary vaccine Barbervax® used against resistant *Haemonchus contortus* in small ruminants, could be incorporated into an integrated control program to combat trichuriasis, which has proven itself to be less responsive to anthelmintic therapy? Perhaps there is some effective anti-parasitic plant out of the 80 plus species of medicinal plants that have been identified as treatments for human helminths [62] that women of reproductive age, school children or adults at risk of hookworm infection could safely consume thereby decreasing morbidity? Or perhaps streamlining fecal diagnostic testing to aid in more targeted, selective anthelmintic treatment of high-risk individuals in certain communities? There are low-cost, rapid (sample preparation and egg counts completed in 5 min), accurate automated egg counters available for point-of-care use by trained community health workers in remote field settings such as the Parasight™ system currently being used for equine strongyles and ascarids [63,64] and qPCR fecal assays that have been shown to correlate highly to a level of STH infection [65]. However, it goes without saying that none of these adjunctive measures will matter in the long-term if the risk of reinfection persists in the environment. In horses, pasture hygiene has been acknowledged for many years as the most effective method of controlling equine parasites, and if feces are removed frequently anthelmintic treatments may not be needed at all [66]. As in veterinary species, the parasite life-cycle must be broken in order to reduce human exposure to STHs. Composting human waste cost-effectively via biogas systems in communities that use human feces as fertilizer in China, or providing low-cost footwear combined with pictorial education in illiterate, hookworm endemic populations in Uganda are two such examples [67,68]. Improved sanitation will interrupt parasite transmission and reduce morbidity.

Holistic parasite control programs that have been successful, such as the LAWA model in Thailand for sustainable liver fluke control [69], or STH control in Sichuan Province in China [70], understand the complexity required for success – they have their basis in the prevention of disease transmission and they recognize the importance of identifying socio-cultural factors and human behaviors that make populations vulnerable to STHs and target these through health education. Such Eco-Health/One Health programs also emphasize the importance of identifying unique ecosystem effects on growth or transmission of STHs to human hosts [69]. The survival of STH larvae vary geographically with environmental conditions (average humidity and temperature, climatic events, and crops) [71] and will also depend on the socio-economic level of the community, times of political unrest, and with population density. For example, in Sichuan Province, 97.5% of total STH infections were found to be in the mountains, plateaus and hilly areas where cultural and economic development lag behind and sanitary conditions are poor [70]. Lastly, successful holistic STH programs recognize the importance of community engagement - health communication and education - by involving local stakeholders within each unique ecosystem who understand the particulars of their environment and culture. In Sichuan Province, STH infection rate was reduced from 82.4% to 3.6% after 5 years of integrated control [70]. Top-down policies, such as the WHO's primary public health intervention in the campaign to eliminate STHs, the preventive chemotherapy approach, are problematic for several reasons – they waste valuable resources and funds, they do not utilize a bottom-up, Eco-Health/One Health approach in communities within a culturally acceptable framework, and they are not breaking the parasite life cycle in a sustainable way.

3. Conclusions

Anthelmintics were not developed to *prevent* parasitism, and the term “preventive chemotherapy” is misleading and naïve as it implies prophylactic use, which is no longer acceptable in veterinary medicine due to the prevalence of anthelmintic resistance. Anthelmintics are meant to be one part of a parasite control program where they are used to *treat* individuals who have been diagnosed with clinical parasitism in order to decrease disease-associated morbidity. Suggestions of decreased anthelmintic efficacy have already been documented in all four currently recommended drugs for STH infections for certain species of STH [15]. If documented anthelmintic resistance occurs during the campaign to eliminate STHs it could result in an even larger scale, global public-health problem for those suffering from infection with STHs as there will be no effective therapeutic options for those with the greatest morbidity. Anthelmintic efficacy must be preserved for as long as possible, and efficacy must be documented through sensitive surveillance methods. Control of human helminthiasis is contingent upon the willingness of those involved in human medicine to look beyond preventive chemotherapy and to the lessons learned in veterinary medicine. As Geerts and Gryseels warned us over 20 years ago [1], continued disregard for their significance could prove disastrous.

Declaration of Competing Interest

The author of this paper has no financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

References

[1] S. Geerts, G.C. Coles, B. Gryseels, Anthelmintic resistance in human helminths: learning from the problems with worm control in livestock, Parasitol. Today 13 (1997) 149–151.

[2] S. Geerts, B. Gryseels, Drug resistance in human helminths: current situation and lessons from livestock, Clin. Microbiol. Rev. 13 (2000) 207–222.

[3] S. Geerts, B. Gryseels, Anthelmintic resistance in human helminths: a review, Tropical Med. Int. Health 6 (2001) 915–921.

[4] T.H. Terrill, J.E. Miller, J.M. Burke, J.A. Mosjidis, R.M. Kaplan, Experiences with integrated concepts for the control of *Haemonchus contortus* in sheep and goats in the United States, Vet. Parasitol. 186 (2012) 28–37.

[5] F. Kenyon, A.W. Greer, G.C. Coles, G. Cringoli, E. Papadopoulos, J. Cabaret, et al., The role of targeted selective treatments in the development of refugia-based approaches to the control of gastrointestinal nematodes of small ruminants, Vet. Parasitol. 164 (2009) 3–11.

[6] F.S. Malan, J.A. Van Wyk, C.D. Wessels, Clinical evaluation of anaemia in sheep: early trials, Onderstepoort J Vet Res 68 (2001) 165–174.

[7] G.F. Bath, J.A. van Wyk, The five point check© for targeted selective treatment of internal parasites in small ruminants, Small Rumin. Res. 86 (2009) 6–13.

[8] R.M. Kaplan, M.K. Nielsen, An evidence-based approach to equine parasite control: it ain’t the 60s anymore, Equine Vet Educ 22 (2010) 306–316.

[9] R.M. Kaplan, Anthelmintic resistance in nematodes of horses, Vet. Res. 33 (2002) 491–507.

[10] R.M. Kaplan, Drug resistance in nematodes of veterinary importance: a status report, Trends Parasitol. 20 (2004) 477–481.

[11] M.K. Nielsen, Sustainable equine parasite control: perspectives and research needs, Vet. Parasitol. 185 (2012) 32–44.

[12] WHO, Integrating Neglected Tropical Diseases into Global Health and Development: Fourth Report on Neglected Tropical Diseases, http://www.who.int/neglected_diseases/resources/9789241565448/en/ accessed December 2017, (2017).

[13] V.A. Welch, E. Ghogomu, A. Hossain, S. Awasthi, Z.A. Bhutta, C. Cumberbatch, et al., Mass deworming to improve developmental health and wellbeing of children in low-income and middle-income countries: a systematic review and network meta-analysis, Lancet Glob. Health 5 (2017) e40–e50.

[14] W.M. Thayer, A. Clermont, N. Walker, Effects of deworming on child and maternal health: a literature review and meta-analysis, BMC Public Health 17 (Suppl. 4) (2017) 830, https://doi.org/10.1186/s12889-017-4747-0.

[15] W. Moser, C. Schindler, J. Keiser, Efficacy of recommended drugs against soil-transmitted helminths: a systematic review and network meta-analysis, BMJ 358 (2017) j4307.

[16] D.C. Taylor-Robinson, N. Maayan, K. Soares-Weiser, S. Donegan, P. Garner, Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin, and school performance, Cochrane Database Syst. Rev. 7 (2015) CD000371.

[17] B. Levecke, A. Montresor, M. Albonico, S.M. Ame, J.M. Behnke, et al., Assessment of anthelmintic efficacy of mebendazole in school children in six countries where soil-transmitted helminths are endemic, PLoS Negl. Trop. Dis. 8 (10) (2014) e3204, , https://doi.org/10.1371/journal.pntd.0003204.

[18] N.C. Sangster, R.J. Dobson, Anthelmintic resistance, The Biology of Nematodes, 1st Ed, Taylor & Francis, London, UK, 2002, pp. 531–567.

[19] J. Vercruysse, M. Albonico, J.M. Behnke, A.C. Kotze, R.K. Prichard, J.S. McCarthy, et al., Is anthelmintic resistance a concern for the control of human soil-transmitted helminths? Int. J. Parasitol. Drugs Drug Resist. 1 (2011) 14–27.

[20] T. Inpankaew, F. Schär, A. Dalsgaard, V. Khieu, W. Chimnoi, C. Chhoun, et al., High prevalence of Ancylostoma ceylanicum hookworm infections in humans, Cambodia, 2012, Emerg. Infect. Dis. 20 (6) (2014) 976–982, https://doi.org/10.3201/eid2006.131770.

[21] GBD 2015 DALYs and Hale Collaborators, Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the global Burden of disease study 2015, Lancet 388 (2016) 1603–1658, https://doi.org/10.1016/S0140-6736(16)31460-X.

[22] I. Wani, M. Rather, G. Naikoo, A. Amin, S. Mushtaq, M. Nazir, Intestinal ascariasis in children, World J. Surg. 34 (2010) 963–968.

[23] L.S. Stephenson, M.C. Latham, E.A. Ottesen, Malnutrition and parasitic helminth infections, Parasitol 121 (Suppl) (2010) 23–38.

[24] L. Mascarini-Serra, Prevention of soil-transmitted helminth infection, J. Global Infect. Dis. 3 (2011) 175–182.

[25] P.J. Hotez, P.J. Brindley, J.M. Bethony, C.H. King, E.J. Pearce, J. Jacobson, Helminth infections: the great neglected tropical diseases, J. Clin. Invest. 118 (2008) 1311–1321.

[26] A. Valentine, A. Wexler, J. Kates, Kaiser Family Foundation, The U.S. Global Health Budget: Analysis of the Fiscal Year 2017 Budget Request, https://www.kff.org/global-health-policy/issue-brief/the-u-s-global-health-budget-analysis-of-the-fiscal-year-2017-budget-request/, (2017).

[27] T.W. Jia, S. Melville, J. Utzinger, C.H. King, X.N. Zhou, Soil-transmitted helminth reinfection after drug treatment: a systematic review and meta-analysis, PLoS Negl. Trop. Dis. 6 (2012) e1621, , https://doi.org/10.1371/journal.pntd.0001621.

[28] L.P. Kahn, M.R. Knox, G.D. Gray, Enhancing immunity to nematode parasites in pregnant and lactating sheep through nutrition and genetic selection, Rec Adv An Nutr Australia 12 (1999) 15–22.

[29] United Nations, We Can End Poverty, Millenium Development Goals and Beyond 2015, http://www.un.org/millenniumgoals/environ.shtml, (2017) accessed December 2017.

[30] R.K. Prichard, M.G. Basanez, B.A. Boatin, J.S. McCarthy, H.H. García, A. Gazzinelli, et al., A research agenda for helminth diseases of humans: intervention for control and elimination, PLoS Negl. Trop. Dis. 6 (2012) e1549, , https://doi.org/10.1371/journal.pntd.0001549.

[31] M.B. Molento, M.K. Nielsen, R.M. Kaplan, Resistance to avermectin/milbemycin anthelmintics in equine cyathostomins- current situation, Vet. Parasitol. 185 (2012) 16–24.

[32] G. Panic, U. Duthaler, B. Speich, J. Keiser, Repurposing drugs for the treatment and control of helminth infections, Int. J. Parasitol. Drugs Drug Resist. 4 (2014) 185–200.

[33] R.M. Kaplan, Recommendations for control of small ruminant parasites, In: Proceedings of the 18th Annual North Carolina Veterinary Conference Raleigh, 2013 North Carolina http://assets.conferencespot.org/fileserver/file/48126/filename/R-Kaplan1.pdf (Accessed January 4, 2014).

[34] R.M. Anderson, J.E. Truscott, R.L. Pullan, S.J. Brooker, T.D. Hollingsworth, How effective is school-based deworming for the community-wide control of soil-transmitted helminths? PLoS Negl. Trop. Dis. 7 (2013) e2027, , https://doi.org/10.1371/journal.pntd.0002027.

[35] D. De Clercq, M. Sacko, J. Behnke, F. Gilbert, P. Dorny, J. Vercruysse, Failure of mebendazole in treatment of human hookworm infections in the southern region of Mali, Am J Trop Med Hyg 57 (1997) 25–30.

[36] J.A. Reynoldson, J.M. Behnke, L.J. Pallant, M.G. Macnish, F. Gilbert, S. Giles, R.J. Spargo, R.C. Thompson, Failure of pyrantel in treatment of human hookworm infections (*Ancylostoma duodenale*) in the Kimberley region of Northwest Australia, Acta Trop. 68 (1997) 301–312.

[37] M. Albonico, Methods to sustain drug efficacy in helminth control programmes, Acta Trop. 86 (2003) 233–242.

[38] C. Flohr, L.N. Tuyen, S. Lewis, T.T. Minh, J. Campbell, J. Britton, et al., Low efficacy of mebendazole against hookworm in Vietnam: two randomized controlled trials, Am J Trop Med Hyg 76 (2007) 732–736.

[39] B. Speich, W. Moser, S.M. Ali, S.M. Ame, M. Albonico, J. Hattendorf, et al., Efficacy and reinfection with soil-transmitted helminths 18 weeks post-treatment with albendazole-ivermectin, albendazole-mebendazole, albendazole-oxantel pamoate and medbendazole, Parasit. Vectors 9 (2016) 123, https://doi.org/10.1186/s13071-016-1406-8.

[40] WHO, Assessing the Efficacy of Anthelminthic Drugs Against Schistosomiasis and Soil-Transmitted Helminthiases, vol. 2013, World Health Organization, Geneva, Switzerland, 2013https://www.who.int/neglected_diseases/resources/9789241564557/en/ (accessed February 2014).

[41] E.T. Lyons, S.C. Tolliver, S.S. Collins, Probable reason why small strongyle EPG counts are returning “early” after ivermectin treatment of horses on a farm in central Kentucky, Parasitol. Res. 104 (2009) 569–574.

[42] P.J. Waller, Resistance to anthelmintics and the implications for animal production, Resistance in Nematodes to Anthelmintic Drugs, CSIRO Division of Animal Health, Australian Wool Corporation, Glebe, Australia, 1985, pp. 1–12.

[43] E.H. Barnes, R.J. Dobson, I.A. Barger, Worm control and anthelmintic resistance: adventures with a model, Parasitol. Today 11 (1995) 56–63.

[44] S.H. Farrell, L.E. Coffeng, J.E. Truscott, et al., Investigating the effectiveness of current and modified world health organization guidelines for the ontrol of soil-transmitted helminth infections, J Clin Infect Dis 66 (4) (2018) S253–S259.

[45] Starworms, https://www.starworms.org/, (2019) , Accessed date: 1 August 2019.

[46] J. Horton, Global anthelmintic chemotherapy programs: learning from history, Trends Parasitol. 19 (9) (2003 Sep) 405–409.

[47] K. Ziegelbauer, B. Speich, D. Mäusezahl, R. Bos, J. Keiser, J. Utzinger, Effect of sanitation on soil-transmitted helminth infection: systematic review and meta-analysis, PLoS Med. 9 (2012) e1001162, , https://doi.org/10.1371/journal.pmed.1001162.

[48] M.C. Freeman, J.V. Garn, G.D. Sclar, S. Boisson, K. Medlicott, K.T. Alexander, et al., The impact of sanitation on infectious disease and nutrition status: a systematic review and meta-analysis, Int. J. Hyg. Environ. Health 220 (2017) 928–949.

[49] L. Fewtrell, R.B. Kaufmann, Z.D. Kay, W. Enanoria, L. Haller, J.M. Colford, Water, sanitation and hygiene interventions to reduce diarrhea in less developed countries: a systematic review and meta-analysis, Lancet Infect. Dis. 5 (2005) 42–52.

[50] E.C. Strunz, D.G. Addiss, M.E. Stocks, S. Ogden, J. Utzinger, M.C. Freeman, Water, sanitation, hygiene, and soil-transmitted helminth infection: a systematic review and meta-analysis, PLoS Med. 11 (3) (2014) e1001620.

[51] D. Abraham, S.P. Kaliappan, J.L. Walson, S.S. Rao Ajjampur, Intervention strategies to reduce the burden of soil-transmitted helminths in India, Indian J. Med. Res. 147 (2018) 533–544, https://doi.org/10.4103/ijmr.IJMR_881_18.

[52] S.J. Campbell, S.V. Nery, J.S. McCarthy, D.J. Gray, R.J. Soares Magalhães, A.C.A. Clements, A critical appraisal of control strategies for soil-transmitted helminths, Trends Parasitol. 32 (2) (2016 Feb) 97–107, https://doi.org/10.1016/j.pt.2015.10.006.

[53] L.E. Coffeng, S. Vaz Nery, D.J. Gray, R. Bakker, S.J. de Vlas, A.C.A. Clements, Predicted short and long-term impact of deworming and water, hygiene, and sanitation on transmission of soil-transmitted helminths, PLoS Negl. Trop. Dis. 12 (12) (2018) e0006758.

[54] S.J. Campbell, N.K. Biritwum, G. Woods, Y. Velleman, F. Fleming, J.R. Stothard, Tailoring water, sanitation, and hygiene (wash) targets for soil-transmitted helminthiasis and schistosomiasis control, Trends Parasitol. 34 (1) (2018) 53–63.

[55] L. Savioli, Preventive anthelmintic chemotherapy–expanding the armamentarium, N. Engl. J. Med. 370 (7) (2014) 665–666.

[56] I. Scott, W.E. Pomroy, P.R. Kenyon, G. Smith, B. Adlington, A. Moss, Lack of efficacy of monepantel against *Teladorsagia circumcincta* and *Trichostrongylus colubriformis*, Vet. Parasitol. 198 (2013) 166–171.

[57] N.C. Sangster, Pharmacology of anthelmintic resistance in cyathostomes: it will occur with the avermectin milbemycins, Vet. Parasitol. 85 (1999) 189–204.

[58] A.F. Trawford, F.A. Burden, J. Hodgkinson, Suspected moxidectin resistance in cyathostomes in two donkey herds at the donkey sanctuary, UK, Proceedings 20th International Conference World Association for Advanced Veterinary Parasitology New Zealand, 2006, p. 196.

[59] K.C. Lange, D.D. Olcott, J.E. Miller, J.A. Mosjidis, T.H. Terrill, J.M. Burke, M.T. Kearney, Effect of sericea lespedeza (*Lespedeza cuneata*) fed as hay, on natural and experimental *H. contortus* infections in lambs, Vet. Parasitol. 141 (2006) 273–278.

[60] K. Healey, C. Lawlor, M.R. Knox, et al., Field evaluation of Duddingtonia flagrans IAH 1297 for the reduction of worm burden in grazing animals: pasture larval studies in horses, cattle and goats. Vet Parasitol 2018;258:124-132.Herd RP. Epidemiology and control of equine strongylosis in Newmarket, Equine Vet. J. 18 (1986) 447–485.

[61] J.B. Noon, R.V. Aroian, Recombinant subunit vaccines for soil-transmitted helminths, Parasitol 144 (2017) 1845–1870.

[62] I.E. Cock, et al., A review of the traditional use of southern African medicinal plants for the treatment of selected parasite infections affecting humans, J. Ethnopharmacol. 220 (2018) 250–264.

[63] P. Slusarewicz, S. Pagano, C. Mills, G. Popa, K.M. Chow, M. Mendenhall, D.W. Rodgers, M.K. Nielsen, Automated parasite faecal egg counting using fluorescence labelling, smartphone image capture and computational image analysis, Int. J. Parasitol. 46 (8) (2016) 485–493.

[64] S.J. Sowerby, J.A. Crump, M.C. Johnstone, K.L. Krause, P.C. Hill, Smartphone microscopy of parasite eggs accumulated into a single field of view, Am J Trop Med Hyg 94 (1) (2016) 227–230.

[65] E.M. O'Connell, T.B. Nutman, Molecular diagnostics for soil-transmitted helminths, Am J Trop Med Hyg 95 (3) (2016) 508–513.

[66] R.P. Herd, Epidemiology and control of equine strongylosis in Newmarket, Equine Vet. J. 18 (1986) 447–485.

[67] J.M. Hawdon, Controlling soil-transmitted helminths: time to think inside the box? J. Parasitol. 100 (2) (2014) 166–188.

[68] S.B. Paige, S. Friant, L. Clech, C. Malave, C. Kemigabo, R. Obeti, T.L. Goldberg, Combining footwear with public health iconography to prevent soil-transmitted helminth infections, Am J Trop Med Hyg 96 (1) (2017) 205–213.71.

[69] S. Tangkawattana, B. Sripa, Integrative eco-health/one health approach for sustainable liver fluke control: the lawa model, Adv. Parasitol. 102 (2018) 115–139.

[70] H. Tian, J. Luo, B. Zhong, Y. Huang, H. Xie, L. Liu, Challenges in the control of soil-transmitted helminthiasis in Sichuan, Western China, Acta Trop. 199 (2019).

[71] L.E. Coffeng, R. Bakker, A. Montresor, et al., Feasibility of controlling hookworm infection through preventive chemotherapy: a simulation study using the individual-based WORMSIM modelling framework, Parasites Vectors 8 (2015), https://doi.org/10.1186/s13071-015-1151-4 541.