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Review article

Monsters in our food: Foodborne trematodiasis in the Philippines and beyond

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Abstract

Foodborne trematodiasis is a neglected tropical disease (NTD) caused by zoonotic trematodes that persist mainly in impoverished areas in the Asia-Pacific region. Globally, about 2 million disability life years (DALYs) are lost due to these parasitic infections. Four groups of foodborne trematodes are known to cause significant illness: fish-borne liver fluke infections caused by *Opisthorchis* and *Clonorchis* spp.; water vegetable-borne *Fasciola* spp. infections; crustacean-vectored paragonimiasis; and those caused by intestinal trematodes. In the Philippines, endemic foodborne trematodes of public health concern include *Paragonimus westermani*, some members of Heterophyidae and Echinostomatidae, and *Fasciola hepatica*/ *F. gigantica*. *Opisthorchis viverrini* and *Clonorchis sinensis* have also been reported in the country. Data on the epidemiology of these zoonotic illnesses remain scarce and in need of research attention in the Philippines. Culturally rooted eating behaviors in endemic areas are important risk factors to acquiring and perpetuating foodborne trematodiasis. The combination of mass drug administration (MDA), provision of clean water and maintenance of good sanitation and hygiene (WASH), community health education towards modification of risky behaviors, surveillance, and veterinary public health interventions have been shown to be effective in combatting these zoonotic parasitoses. An integrated control and prevention program anchored on the One Health paradigm is a must to address these illnesses. This paper aims to review the biology and epidemiology of, and public health interventions against zoonotic foodborne trematodiasis in the Philippines and its neighboring countries.

Keywords: Foodborne Trematodes, Neglected Tropical Diseases, Philippines, One Health, Veterinary Public Health

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INTRODUCTION

Foodborne trematodiasis is a group of zoonotic parasitoses caused by flukes that are vehicled by poorly prepared food items (Keiser and Utzinger, 2009; Lu et al., 2018; Betson et al., 2020). This group of parasitic infections is one of the illnesses classified by the World Health Organization as Neglected Tropical Diseases (NTDs) (Engels and Zhou, 2020; Nguyen et al., 2021; Casulli, 2021). NTDs plague impoverished, rural areas in developing countries where hygienic practices and cultural eating behaviors are conducive to their perpetuation (Belizario et al., 2013; Engels and Zhou, 2020). Annually, more than 750 million people are at risk and approximately 2 million disability life years (DALYs) are lost worldwide due to foodborne trematodiasis (Keiser and Utzinger, 2009; World Health Organization, 2020). It was reported that in 2005, 56.2 million people succumbed to foodborne trematodiasis, with about 7.2 million having severe sequelae, and at least 7000 died worldwide (Fürst et al., 2012a).

Globally, four groups of foodborne trematode infections are known to cause significant diseases: fish-borne liver fluke infections caused by *Opisthorchis* and *Clonorchis* spp.; water vegetable-borne *Fasciola* spp. infections; crustacean-vectored paragonimiasis; and those caused by intestinal trematodes (Yoshida et al., 2019; World Health Organization, 2020; Na et al., 2020). In the Philippines, prevalent foodborne trematodes of public health concern include *Paragonimus westermani*, some members of Heterophyidae and Echinostomatidae, and *Fasciola hepatica*/ *F. gigantica* (Balderia and Belizario, 2012; Leonardo et al., 2020). However, it has been noted that among the NTDs in the country, foodborne trematodiasis is one of the most underreported and thus understudied; sparse epidemiologic studies were published and need updating (Leonardo et al., 2020).

This paper aims to review the occurrence and epidemiology of zoonotic foodborne trematodiasis in the Philippines and its neighboring countries. Each trematode's biology, transmission dynamics, treatment, prevention, control and elimination are briefly subsumed herein.

THE MONSTERS: The Etiologic Agents, Transmission Dynamics and Epidemiology

As their name implies, foodborne trematodes can infect humans and other susceptible animals when they inadvertently consume food items containing the parasites' infective stages. Depending on the trematode's life cycle, various types of foods carry their infective metacercariae (i.e., infective stage). These food items may serve as the second intermediate hosts (i.e., metacercaria encysts in its tissues): freshwater fishes for opisthorchiasis, clonorchiasis and heterophyidiasis; edible snails, fishes, and amphibians for echinostomiasis; and crustaceans for paragonimiasis. Sometimes, the food vehicles are not part of the trematode's life cycle, but their metacercariae attach on these food items to be ingested by a mammalian host: water vegetables in the case of fasciolosis. In general, these parasites require a mammalian final host, where reproductive maturity and egg-laying will occur. Further discussions on the specifics of each foodborne trematode are provided in the subsequent subsections of this review.

Paragonimiasis

Lung flukes of the genus *Paragonimus* are the etiology of paragonimiasis. The infection is acquired via consumption of improperly cooked, infected crustaceans – the second intermediate host (Waikagul et al., 2015; Yoshida et al., 2019). The disease has a wide distribution in regions of tropical and subtropical climates (Yoshida et al., 2019). There are more than 70 species currently identified, among which, *P. westermani*, *P. heterotremus*, and *P. skrjabini* are the most common agents of human paragonimiasis in Asia (Yoshida et al., 2019; Nakagawa et al., 2021; Tantrawatpan et al., 2021). It has been posited that more than 20 million people succumb to paragonimiasis worldwide, with about 293 million people at risk of acquiring the parasitosis (Keiser and Utzinger, 2009).

Infections in the Philippines are caused by *P. westermani* (Belizario et al., 1997; de Leon and Piad, 2005). *Paragonimus siamensis* is the only other lung fluke recorded in the country; it has only been found in cats (Cabrera and Vajrasthira, 1972; Cabrera and Vajrasthira, 1973; Cabrera, 1984). In the late 1970s, it was reported that there was a third *Paragonimus* species in the country – *P. philippinensis* (Ito et al., 1978). However, it was later relegated to be a subspecies of *P. westermani* (Miyazaki and Habe, 1979). Paragonimiasis remains a public health concern in Mindoro, Camarines Sur, Sorsogon, Samar, Leyte, Zamboanga del Norte, Davao region, Cotabato Province, and Basilan (Belizario et al., 2014a; Belizario et al., 2016). Recently, delos Trinos et al. (2020) reported paragonimiasis prevalences of 5.24% (7/153) in two municipalities in Zamboanga del Norte, 22.06% (15/68) in one municipality in Zamboanga del Sur, and 7.7% (29/373) in one municipality in Zambaonga Sibugay. *Jagora (Antemelania) asperata* and *J. (A.) dactylus* snails serve as trematode's first intermediate hosts and *Sundathelphusa philippina* is the crustacean second intermediate host in the country (Eduardo, 2001; Paller et al., 2021). Recently, Paller et al. (2021) reported that 41.87% of the 246 *S. philippina* crabs collected from Irosin, Sorsogon were infected with *P. westermani* metacercariae. The infective stages were found in the crabs' gills and muscle tissues (Paller et al., 2021). Moreover, a snail infection rate of 12% was found among *Tarebia granifera* and *J. asperata* snails from the same area (Paller et al., 2021). In the eastern parts of the Philippines, including Sorsogon, Samar and Leyte, consumption of the local delicacy called kinagang – steamed crab meat and rice wrapped in banana leaf with fresh crab juice – has been noted to be an important risk factor for paragonimiasis (Eduardo, 2001; Leonardo et al., 2020).

Clinical signs of paragonimiasis are elicited due to the migration of and immune response against the lung flukes – eosinophilic inflammation around the trematodes results (Yoshida et al., 2019). Pulmonary paragonimiasis induces pleuritis, pneumonia, and/or bronchitis that is manifested by cough and hemoptysis that develop to inflammatory infiltration and nodular lesions seen in chest radiography (Nagayasu et al., 2015). Cerebral paragonimiasis may also occur (Xia et al., 2016). Pulmonary paragonimiasis share most of its clinical manifestations with Pulmonary Tuberculosis (PTB) (Yoshida et al., 2019; Leonardo et al., 2020). Misdiagnosis of *P. westermani* infections as PTB that is resistant to conventional treatment plans is not uncommon in endemic areas in the Philippines (Belizario et al., 1997; Belizario et al., 2016; delos Trinos et al., 2020).

Fasciolosis

Fasciolid liver flukes are the cause of fasciolosis. The disease has a worldwide distribution (Cwiklinski et al., 2016; WHO, 2020). It has been reported that more than 2.4 million individuals are affected by this zoonotic infection worldwide (Cwiklinski et al., 2016). *Fasciola hepatica* and *F. gigantica* are the predominant species that cause significant illnesses in humans and ruminants (i.e., cattle, sheep, and goats); the former trematode is found in temperate regions, and the latter causes fasciolosis in tropical countries (Molina et al., 2005; Phalee and Wongsawad, 2014; Portugaliza et al., 2019; Jumawan et al., 2020; Corrales et al., 2021). The snail intermediate hosts of the trematode in the Philippines are *Radix (Lymnaea) philippinensis* and *R. (L.) auricularia rubiginosa* (Eduardo, 2001; Molina et al., 2005; Betson et al., 2020). It is transmitted through the consumption of improperly washed raw vegetables that are grown in or near bodies of water cohabitated by ruminants and snail intermediate hosts (Cwilinski et al., 2016; Sah et al., 2018; World Health Organization, 2020). In the Philippines, two cases were initially reported that were thought to be caused by consumption of improperly prepared *kangkong (Ipomoea aquatica)* or other water vegetables (Figure 1B) (Eduardo, 2001). In both humans and animals, fasciolosis occurs in two phases: acute or invasive phase and chronic or latent phase (Fürst et al., 2012b, Leerapun et al., 2021) Acute fasciolosis symptoms occur due to the migration of immature flukes, while liver abscesses leading to the development 'pipestem' fibrosis are seen in chronic cases (Fürst et al., 2012b; Leerapun et al., 2021). A recent study found that abdominal pain, weight loss and fever were the most common symptoms encountered by patients with hepatic abscesses due to fasciolosis (Leerapun et al., 2021). Research on human fasciolosis is wanting and needs more attention in the Philippines (Leonardo et al., 2020).

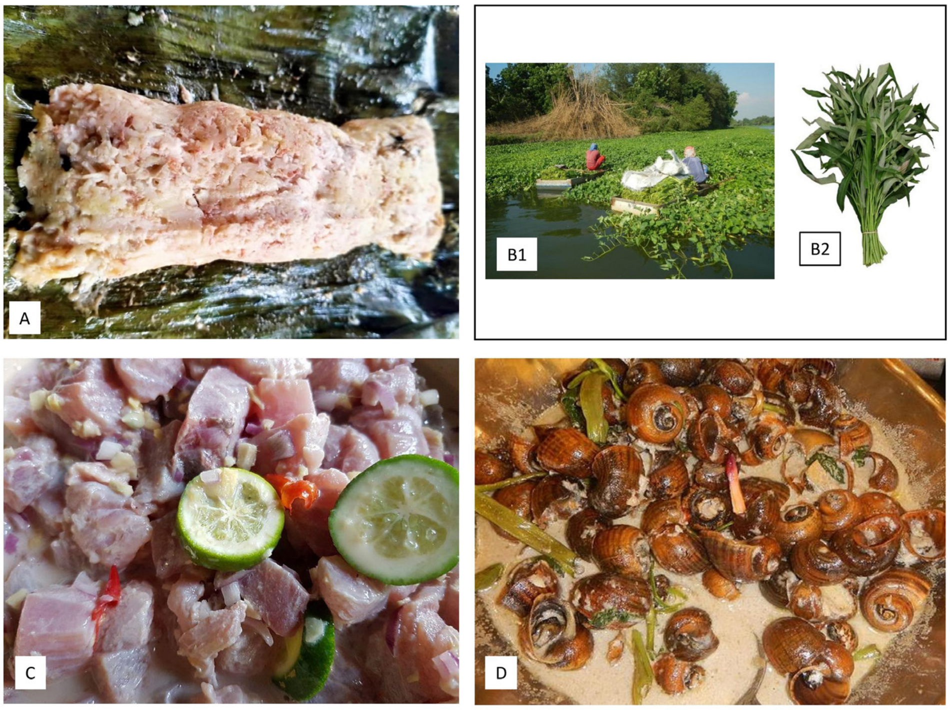

Figure 1 Food items implicated to be the vehicles foodborne trematodes in the Philippines. *Kinagang* is a delicacy in eastern parts of the country and is prepared by steaming rice with crab meats and juices (A). Consumption of the food item has been linked to higher risks of acquiring paragonimiasis. Kangkong or water spinach (*Ipomoea aquatica*) grows primarily in or near bodies of water where the metacercariae of *Fasciola* spp. can attach to them (B1). They are sold in bundles in the Philippines (B2). *Kinilaw* is a fish dish similar to ceviche (i.e., prepared with vinegar and/or lime) that is eaten raw (C). This food item is a significant risk factor for heterophydiasis in the southern Philippines. *Bisokol* or apple snails are edible snails cooked in various ways and are particularly popular in the northern and eastern Philippines (D). Consumption of improperly cooked *bisokol* increases the risk of acquiring echinostomiasis.

Opisthorchiasis and Clonorchiasis

Opisthorchiasis and clonorchiasis are infections caused by the consumption of freshwater cyprinid fishes that carry the encysted metacercaria in their flesh or under their scales (Hung et al., 2013; Nithikathkul et al., 2021). Opisthorchiasis in the Asia-pacific region is caused by *Opisthorchis viverrini* and *O. felineus* (Sithithaworn et al., 2012; Waikagul et al., 2015; Xin et al., 2020; Zhao et al., 2021). The former is endemic in the Mekong River basin in Cambodia, Lao PDR, and northern Thailand (Waikagul et al., 2015; Phupiewkham et al., 2021; Kitphati et al., 2021). Approximately 90 million people in Southeast Asia have been posited to be at risk of acquiring *O. viverrini* infections, with about 10 million already being affected (Nithikathkul et al., 2021). The only case of opisthorchiasis reported in the Philippines was from Davao – the adult parasite was found in the bile ducts of a surgical patient (Belizario and Ciro, 2020). Dogs and cats are also susceptible to *O. viverrini* infections and are regarded as important reservoirs of human infections in Thailand and Vietnam

(Aunpromma et al., 2012, 2016; Tangkawattana and Tangkawattana, 2018). A recent systematic review and metanalysis revealed that male sex, young age (< 24 years), older age (> 55 years), low educational attainment, being a laborer and farmer, living near the Mekong River, having pet dogs and cats, and previous infection and praziquantel intake were associated with *O. viverrini* infections (Pengput and Schwartz, 2020). *Clonorchis sinensis* is the etiology of clonorchiasis, a disease that occurs in China, Korea, Japan, Taiwan, Thailand, Vietnam, and eastern Russia (Waikagul et al., 2015; Nguyen et al., 2020). Approximately 15 million people are at risk, with 2 million being affected worldwide (Waikagul et al., 2015; Zhu et al., 2020; Na et al., 2020). In the Philippines, clonorchiasis has been reported in 135 stool samples from different parts of the country; eggs with similar morphology to *C. sinensis* were detected (Cross and Basaca-Sevilla, 1984). These foodborne liver flukes are transmitted by undercooked native fish dishes: *pla-ra* (fermented fish), *pla-som* (fermented sour fish) in Thailand; *sushi* and *sashimi* in Japan (Chai and Jung, 2017; Na et al., 2019). Increasing age (> 30 years), and consumption of underprepared fish dishes at home were the risk factors noted for clonorchiasis in China according to a recent survey (Xin et al., 2021).

The severe pathologies of opisthorchiasis and clonorchiasis in the hepato-biliary system lead to the development of cholangiocarcinoma (Betson et al., 2020; Zhu et al., 2020). *Clonorchis sinensis* and *O. viverrini* are considered group 2A carcinogens by the International Agency for Research on Cancer (IARC) (Betson et al., 2020). Individuals that had succumbed to opisthorchiasis and clonorchiasis are at higher risk of developing cholangiocarcinoma; frequency of cholangiocarcinoma is positively correlated to infection and area of endemicity of *O. viverrini* and *C. sinensis* (Khuntikeo et al., 2018; Sripa et al., 2018).

Minute Intestinal Trematodes

This group of trematodes are composed primarily of those belonging to the helminth families Heterophyidae and Echinostomatidae – these are the most important causes of human infections (Betson et al., 2020). It is believed that more than 50 million people are infected in Southeast Asia, but true burden may be severely underestimated (Chai and Jung, 2017).

Four heterophyid species have been recorded to cause infections among Filipinos: *Haplorchis taichui*, *H. yokogawai*, *Procerovum calderoni* and *Stellanthchasmus falcatus* (Eduardo, 2001; Chai and Jung, 2017). *Haplorchis taichui* uses *Stenomelania (Melania) juncea*, while *P. calderoni* uses *Sermyla (Thiaria)* riquetti as their first snail intermediate hosts (Eduardo, 2001; Chai and Jung, 2017). Moreover, many common food fishes have been shown to harbor the infective metacercariae of these trematodes, including but not limited to *dalag (Channa striata)*, *bangus (Chanos chanos)*, *hito (Clarias batrachus)*, *lapu-lapu (Epiohelus corollicola)*, and tilapia (*Oreochromis niloticus*) (Eduardo, 2001; Mahdy et al., 2021; El-Seify et al., 2021). The snakehead murrel (*Channa striata*) is the second intermediate host, and dogs and cats serve as the natural definitive host of *P. calderoni* in China, Egypt, and the Philippines (Chai and Jung, 2019).

Haplorchis taichui have been reported to be prevalent in Mindanao (Belizario et al., 2004; Leonardo et al., 2008). Recently, Moendeg et al. (2021) reported a heterophyid infection prevalence of 2.36% (26/1,101) in Davao del Norte. They also found that male gender, eating raw freshwater fish and undercooked grilled fish, and living near bodies of water were significantly associated with heterophyidiasis (Moendeg et al., 2021). In Thailand and Laos, consumption of underprepared fish dishes has been noted to be an important risk factor for heterophyidiasis (Chai and Jung, 2017). This parasite reportedly caused abdominal pain, diarrhea, malaise, and peptic-ulcer-like illness; affected individuals have a habit of eating uncooked fish salad (i.e., *kinilaw*) (Figure 1C) (Belizario et al., 2004).

Echinostomiasis, caused by *Echinostoma ilocanum* and *Artyfechinostomum (E.) malayanum*, is said to be endemic in Luzon, Leyte, Samar, and Mindanao (Belizario et al., 2007; Leonardo et al., 2020). *Echinostoma ilocanum* requires two sets of freshwater snails to complete its lifecycle: *Gyraulus convexiusculus* and *Hippeutis umbilicalis* serve as the first intermediate hosts, while *Pila luzonica* and *Sinotaia (Vivipara) angularis* are the second intermediate hosts (Eduardo, 2001; Belizario and Balderia, 2012; Toledo and Esteban, 2016). *Bullastra cumingiana*, *Radix quadrasi*, and *Physa (Physastra) hungerfordiana* have been identified as snail intermediate hosts of *A. (E.) malayanum* in the Philippines (Monson and Kitikoon, 1992; Belizario et al., 2007). The confirmed second intermediate host of *A. (E.) malayanum* in the Philippines are *B. cumingiana* and *Pomacea canaliculata (Ampullaris canaliculatus)* (Balderia and Belizario, 2012). Frogs, tadpoles, and some freshwater fishes may also serve as the second intermediate hosts (Toledo and Esteban, 2016). Together with humans, rats and dogs are the natural definitive hosts of *E. ilocanum*, while pigs, dogs, rodents, and cats are known to play the same role for *A. (E.) malayanum* (Chai and Jung, 2019). Affected individuals have histories of consuming raw or improperly cooked freshwater snails, primarily *P. luzonica* (Leonardo et al., 2020). The snail is known locally as *bisokol*, which is often eaten partly cooked in northern parts of the Philippines (Figure 1D) (Eduardo, 2001; Leonardo et al., 2020). In southern parts of the country, eating of raw edible snails that are prepared with coconut milk and lime juice, and ill-prepared fish dishes have been linked to echisnostomiasis (Belizario et al., 2007). Consumption of similar, poorly cooked local fish delicacies in Thailand, China, South Korea, and Indonesia have also been cited to be important sources of infections (Toledo and Esteban, 2016). It is also important to note that amphibians may harbor echinostomatid metacercariae, thus consumption of these may also cause illness (Chai and Jung, 2019). Echinostomiasis causes mucosal ulceration, inflammation and hemorrhage in the duodenum and jejunum through the fluke's collar spines, and oral and ventral suckers (Toledo and Esteban, 2016; Chai et al., 2018). Absorption of the trematode's metabolic by-products may lead to general intoxication (Belizario et al., 2007; Chai et al., 2018). Also, diarrhea, marked malnutrition and anemia leading to death can be caused by infections of high trematode burden (Toledo and Esteban, 2016; Chai et al., 2018).

LOOKING FOR THE MONSTERS: Foodborne Trematodiasis Diagnostics

Diagnosis of foodborne trematodiasis is commonly through microscopy of fecal, sputum, and food item samples to detect trematode eggs. Two fecal kato-katz smear preparations are indicated in clinical diagnosis and surveillance sampling (Belizario et al., 2014b; World Health Organization, 2020). Detection of trematode eggs in bronchioalveolar lavage fluid (BALF), sputum, and pleural effusion may also be done to diagnose paragonimiasis (Nagayusa et al., 2015). The value of using Ziehl-Neelsen staining technique in detecting *Paragonimus* ova in sputum specimens was evaluated by delos Trinos et al. (2020). The authors reported that the staining technique had poor sensitivity but excellent specificity and thus concluded that adding a concentration technique may increase its diagnostic performance (delos Trinos et al., 2020). In detecting foodborne parasites in food items, the sedimentation technique has been used, especially in leafy vegetables (Ordoñez et al., 2018; Afable et al., 2019). Microscopic examination of fish and crustacean tissues have been utilized to detect infective stages of fish-borne trematodiasis and paragonimiasis, respectively (Wai et al., 2019; Nithikathkul et al., 2020; Paller et al., 2021). Heterophyids, *Clonorchis* and *Opisthorchis* metacercarae can be detected in the tissues of freshwater fishes either via tissue compression technique or digestion technique (Touch et al., 2013; Boonmekam et al., 2016). The relative ease of performing parasitological techniques and the lack of expensive complicated equipment are the advantages of these tests that make them suitable for field use, especially in financially challenged endemic foci. However, its diminished diagnostic value as endemicity lessens, its incapability of early infection detection, and the expertise needed to accurately identify trematode eggs undermine the wide use microscopy-based diagnostic techniques.

Serodiagnosis of foodborne trematodes requires the detection of antibodies directed towards parasite-derived antigens. Enzyme-linked immunosorbent assays (ELISA) that use somatic extracts from mature *Paragonimus* are the most widely used test for diagnosing paragonimiasis in Japan (Yoshida et al., 2019). Recombinant proteins, such as the CE3, have been used to develop new ELISA assays that reportedly had good sensitivity and specificity in Thailand (Pothong et al., 2018). Similarly, ELISA assays that detect coproantigens have been used to diagnose fasciolosis in animals like sheep and cattle (George et al., 2017; Munita et al., 2019). ELISA tests for fasciolosis that used recombinant cathepsin L, and Fas 1 and Fas 2 cystiene proteases as targets for *F. hepatica* and *F. gigantica*, respectively, had yielded superior sensitivities and specificities (Gonzales-Santana et al., 2013; Rabee et al., 2013). Recently, an ELISA assay that utilized the recombinant cathepsin L1 protein have been described for the diagnosis of fasciolosis in humans caused by the *F. hepatica/gigantica* hybrid type (Sugiyama et al., 2021). Indirect ELISA that detects crude somatic extracts and excretory-secretory antigens are preferred in the diagnosis of opisthorchiasis and clonorchiasis (Khuntikeo et al., 2018; Hong and Fang, 2021; Phupiewkham et al., 2021). In general, serological techniques have superior diagnostic performance when compared to microscopy-based parasitological methods, and are able to detect infections as early as 2 to 4 weeks of infection (Sripa et al., 2010). However, their inability to discriminate current infection from past exposure is a drawback (Khuntikeo et al., 2018). Moreover, the expensive equipment, kits, and reagents needed to conduct these tests add to the difficulty of using them routinely in resource-lacking endemic areas.

Molecular diagnosis of foodborne trematodiasis require the detection of specific parasite genes in samples through polymerase chain reaction (PCR) and its various iterations. A PCR assay that targeted the Internal Transcribed Spacer (ITS) regions in the ribosomal DNA of *O. viverrini*, *C. sinensis*, *H. pumilio*, and *H. taichui* was described by Sato et al. (2009), and used by Li et al. (2019) to diagnose a case of multiple foodborne trematode infections with systemic involvement in Shandong Province, China. To diagnose opisthorchiasis and haplorchiasis, a combined conventional PCR and real-time PCR assay that sequenced the cytochrome c oxidase 1 (*cox-1*) gene was developed by Lamaningao et al. (2017). A simplex and a duplex PCR assays that targeted the second ITS (*ITS-2*) gene of *F. hepatica* and the NADH dehydrogenase 2 (*nad2*) gene of *C. sinensis* were found to have good diagnostic performance in detecting infections in sheep (Yang et al., 2015). Aside from PCR-based techniques, Loop-mediated isothermal amplification (LAMP) assays have been developed as a cheaper alternative with comparable diagnostic performance. A LAMP protocol that targeted the second ITS (*ITS-2*) gene in the ribosomal DNA of *P. westerani* reportedly was 100 times more sensitive than conventional PCR using human and animal fecal samples (Chen et al., 2011; García-Bernalt Diego et al., 2021). Also, LAMP assays with great diagnostic performance have been described for the rapid detection and diagnosis of *O. viverrini* and *C. sinensis* using *ITS-1* and cytochrome c oxidase 1 (*cox-1*) genes, respectively, using stool samples (Arimatsu et al., 2012; Rahman et al., 2016). The high sensitivity and specificity, the capability to detect foodborne trematodes early in the disease course, and the possibility of conducting subsequent molecular analyses (e.g., phylogenetic analysis) are some of the valuable advantages that molecular techniques hold. Moreover, the gene targets used to diagnose these trematodiases in mammalian hosts may also be used to molecularly detect contaminants in food vehicles. However, the expensive cost of equipment and reagents needed for PCR-based assays, and the extensive training for diagnosticians impede its routine use in financially challenged endemic countries, like the Philippines. LAMP assays for foodborne trematodiasis indeed offer rapid, sensitive, and specific results without the need for sophisticated equipment which make them more suitable than PCR in impoverished endemic areas, but their diagnostic performance in the field for surveillance and routine diagnostic use has yet to be validated (García-Bernalt Diego et al., 2021).

DEFEATING THE MONSTERS: Treatment, Prevention, Control and Elimination

Various drugs have been used to manage specific infections caused by foodborne trematodes (Table 1). Moreover, these drugs have also been utilized in Mass Drug Administration (MDA) programs to prevent and control infections (World Health Organization, 2020). Clinical treatment and MDA of infected animal reservoir hosts (i.e., ruminants in the case of fasciolosis; carnivores in the case of opisthorchiasis, clonorchiasis and paragonimiasis) have also been advocated to reduce the sources of trematode eggs (Sripa et al., 2010; Waikagul et al., 2015). Triclabendazole has been used to address *Fasciola* infections in ruminant livestock animals at doses of 5 to 10 mg/kg for sheep and goats, and 12 mg/kg for cattle and water buffaloes given PO or SC; these doses may also be used as chemoprophylaxis administered at 8 to 10 weeks interval in areas of high fasciolosis burden (Constable et al., 2017). However, care must be practiced in the routine use of the drug in order to subvert the development of antiheminthic resistance that has been well-documented for *F. hepatica* (Venturina et al., 2015; Cwilinski et al., 2016; Merachew and Alemneh, 2020). Clinical treatment of opisthorchiasis and clonorchiasis in dogs and cats involve the administration of praziquantel at 20 to 30 mg/kg/day for 3 days (Peregrine, 2014). An alternative treatment against *O. viverrini* in dogs is fenbendazole given at 200 mg/kg/day for 3 days (Peregrine, 2014). Similarly, Praziquantel at 23 mg/kg PO q8h for 3 days has also been found to be effective in addressing clinical paragonimiasis in dogs and cats (Bowman et al., 1991).

Table 1 Summary of the transmission dynamics, treatment, control, elimination, and prevention strategies against foodborne trematodiasis. Treatment and MDA regimens were lifted from World Health Organization (2020).

Foodborne trematodiasis	Etiologic agent	Food vector	Animal definitive hosts	Treatment	Control and prevention strategies
Opisthorchiasis	*Opisthorchis viverrini, O. felineus*	Cyprinid fishes	Cats, Dogs	Praziquantel 25 mg/kg thrice daily for 2-3 days; MDA: 40 mg/kg single administration	Avoid ingestion of raw/ undercooked fish, health education and promotion geared towards dietary behavior modification and elimination of open defecation, capacity building of local health personnel on diagnosis and treatment.
Clonorchiasis	*Clonorchis sinensis*	Cyprinid fishes	Dog, Cats, Pigs, Minks, Rats, Weasels	Praziquantel 25 mg/kg thrice daily for 2-3 days; MDA: 40 mg/kg single administration	Avoid ingestion of raw/ undercooked fish, health education and promotion geared towards dietary behavior modification and elimination of open defecation, capacity building of local health personnel on diagnosis and treatment.
Fasciolosis	*Fasciola gigantica, F. hepatica*	Aquatic vegetables	Cattle, Water Buffaloes, Sheep and Goats	Triclabendazole 10 mg/kg single or 20 mg/kg in 2 doses every 12-24 hours; MDA: Triclabendazole 10 mg/kg single administration	Thorough washing of leafy vegetables and boiling of water prior to ingestion, molluscicides and natural predation to control snail intermediate hosts, community education, capacity building of local health personnel on diagnosis and treatment, human and animal surveillance studies.

Table 1 Summary of the transmission dynamics, treatment, control, elimination, and prevention strategies against foodborne trematodiasis. Treatment and MDA regimens were lifted from World Health Organization (2020). (Cont.)

Foodborne trematodiasis	Etiologic agent	Food vector	Animal definitive hosts	Treatment	Control and prevention strategies
Paragonimiasis	*Paragonimus westermanii*	Crustaceans	Cats, Dogs, Tigers, Opossum, Mongoose, Weasel, Mink, Rat	Triclabendazole 10 mg/kg twice in 1 day or Praziquantel 25 mg thrice a day for 3 days; MDA: Triclabendazole 20 mg/kg single administration	Avoid ingestion of raw/ undercooked crustacean dishes, health education and promotion geared towards dietary behavior modification and elimination of open defecation, capacity building of local health personnel on diagnosis and treatment, human, snail intermediate host, and crustacean surveillance studies.
Minute Intestinal Trematodes	Heterophyidae	Cyprinid Fish	Dogs, Cats, Piscivorous birds	Praziquantel at 75 mg/kg divided in to 3 doses given in a single day.	Avoid ingestion of raw/ undercooked fish and/or snails, health education and promotion geared towards dietary behavior modification and elimination of open defecation, capacity building of local health personnel on diagnosis and treatment, human and intermediate host surveillance studies.
	Echinomastidae	Edible snails, fishes, and amphibians			

Provision of safe and clean water, and implementation of proper sanitation and hygiene (WASH) have also been pointed out to be of value in controlling and preventing these illnesses (Sripa et al., 2010, 2017). Community health education towards behavioral changes regarding these infections have been of benefit in controlling the disease in other parts of Southeast Asia. Changes in community behaviors such as eliminating open defecation and eating of raw fish, undercooked crustaceans or unwashed vegetables have been advocated with much success in reducing infections (Sripa et al., 2017; World Health Organization, 2020; Kitphati et al., 2020).

In the Philippines, efforts to control foodborne trematodiasis have been in the form of integrated programs that aim to lessen the burden of helminthiases among at risk individuals in endemic areas in the country. An example of such initiatives is the Integrated Helminth Control Program (IHCP) that was launched in 2006 and was aimed to provide policy direction to control soil-transmitted helminths and other helminthiases in the country (Philippine Department of Health, 2006). The provision of WASH through providing access to safe water, community toilets and latrines, and school supervised WASH practices were enacted by Local Government Units (LGUs), the Department of Interior and Local Government (DILG), the Department of Health (DOH) and the Department of Education (DepEd) under the auspices of the IHCP (Philippine Department of Health, 2006). Another WASH program that was implemented in 2007 was the Community-Led Total Sanitation (CLTS) that advocated for zero-open defecation, the provision and routine use of toilets, frequent hand washing, practice of hygienic food preparation, proper disposal of waste, and ensuring a clean and safe environment for the entire community (Philippine Department of Health, 2010). School-based WASH initiatives included the implementation of the Essential Health Care Program (EHCP) and WASH in Schools (WINS) program – these provided safe water, deworming, and education on sanitation, food handling and preparation, and hygienic practices improvement to primary school pupils (Philippine Department of Education, 2009, 2016; Belizario et al., 2013). In 2019, the 2019-2023 Food and Water–Borne Disease Prevention and Control Program and Strategic Plan was launched. It is the continuation of the initial program that was launched in 1997 that aimed to reduce the occurrence and eliminate death due to diarrheal pathogens, including foodborne trematodes (Philippine Department of Health, 2019). The plan includes the development of clinical practice guidelines for the management of foodborne trematodiasis and efforts to increase the capability of rural health units to effectively diagnose these illnesses through capacity building and training (Philippine Department of Health, 2019). The strategic plan is also supported by the enactment of the Food Safety Act of 2013 by the Philippine legislature (Betson et al., 2020).

DISCUSSION

Foodborne trematodiasis remains a public health concern in Southeast Asia. Despite being dubbed as an NTD that affect those who have the least in society, very little attention is given to this group of foodborne pathogens. In the Philippines, there are several problems that hamper the elimination of these zoonotic parasitosis. Research remains scarce on foodborne trematodiasis. The actual burden of these zoonotic illnesses is still unknown in the country. Epidemiologic studies are needed to fill-in this research gap. Anent to this, surveillance and risk mapping efforts must be enacted, and thereafter strengthened, in order to accurately pinpoint areas where these diseases are prevalent. These data will be critical in the formulation of appropriate future control and prevention programs. Another problem raised by various research is that foodborne trematodiasis had long been forgotten in endemic areas to the point that they have been confused with other co-existing severe illnesses of similar symptomologies. An example of this is the misdiagnosis of pulmonary paragonimiasis as PTB that is resistant to conventional treatment. This might have arisen due to the lack of capacity to effectively diagnose this foodborne parasitosis in rural, resources-lacking endemic areas. This lack of accurate diagnostic capacity has been posited to contribute to the diminished attention to all foodborne trematodes. Indeed, we hope that efforts to enhance the practice of healthcare providers and diagnostic capabilities of facilities – through trainings and the creation of the clinical practice guidelines – will have a true and lasting impact in addressing the inattention foodborne trematodiasis gets in the country. Also, unsafe eating behaviors – often the norm in endemic areas – like eating ill-prepared fishes, crustaceans, mollusks and vegetables must be changed through rigorous community health risk education. Community folks must be informed of the parasites' lifecycle, risky behaviors that increase likelihood of infection, and how they can control and prevent such infections. In addition, the practice of open defecation must be addressed by continuing the provision of sanitation and hygiene facilities and advocating their routine use. And lastly, risky agricultural practices such as using night soil and animal manure as fertilizers in horticulture and nitrogenous sources in aquaculture should stop. Income earning efforts that reduce environmental helminth ova contamination from fecal materials like composting and biogas processing may be taught in endemic communities.

Along with the call for more research on these pathogens, control and prevention efforts must be strengthened by the local and national government. The previously mentioned integrated helminthiasis control and prevention programs must be intensified and broaden to also include measures that are not WASH and MDA centered. Moreover, funding of basic and applied research on foodborne trematodiasis and other NTDs must be increased to continue the previous work that has been laid by past researchers and academics. And more importantly, funding of control, prevention, and eventually elimination, thrusts must also be secured so that surveillance, the continued roll-out of MDA, construction of WASH facilities (i.e., community toilets and latrines), creation and procurement of community education paraphernalia, capacity training of local healthcare workers, and enactment of veterinary public health mitigation efforts will be guaranteed until health goals on these diseases are achieved. The support of the national and local politicians through legislations, policy crafting and enactment, and financing of control and elimination efforts will be crucial in ridding the country of these NTDs.

An integrated control and prevention program that is anchored on the One Health paradigm is a must in addressing foodborne trematodiasis. The combination of MDA, WASH, community health education towards behavioral changes, surveillance, and veterinary public health interventions have been shown to be effective in combatting these zoonotic parasitic infections. The efficacy of this combo of mitigation efforts is best exemplified by the Lawa Model against opisthorchiasis in northern Thailand (Sripa et al., 2017). Existing community health education thrusts addressed at reducing the risk of NTDs like foodborne trematodiasis should be strengthened by engaging different types of media in endemic areas: print, television, radio, and social media. Also, controlling the infections in the animal hosts via veterinary surveillance and antihelminthic treatments and/or MDA may also be instituted to remove all possible non-human sources of trematode eggs. The control and elimination efforts against foodborne trematodiasis may also be enacted in tandem with similar efforts against other co-prevalent NTDs as a cost-effective and logistics-cutting strategy. Such integrated, inter-disciplinary programs must engage concerned community and their leaders, medical professionals, veterinarians, and environmental scientists to address all aspects of the trematodes' transmission dynamics.

CONCLUSIONS

Several trematode infections contracted via the consumption of infected or contaminated food articles remain a significant health problem globally, especially in financially challenged areas. Eating raw and/or inadequately prepared food items – often the cultural norms in endemic areas – continue to perpetuate these neglected and misdiagnosed infections. Much research to decipher the epidemiology of these parasitoses and strengthening of the Philippines' national and local control and elimination efforts are needed. Foodborne trematodiasis elimination in the country can perhaps be a reality through enacting measures anchored on a truly One Health approach.

STATEMENT OF COMPETING INTERESTS

The authors have no competing interests to declare.

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AUTHOR CONTRIBUTIONS

JCBT conceptualized and wrote the manuscript. ECM critically reviewed and revised the manuscript. All the authors read and approved the manuscript for publication.

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