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Invited review

Fish-borne parasitic zoonoses: Status and issues

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Abstract

The fish-borne parasitic zoonoses have been limited for the most part to populations living in low- and middle-income countries, but the geographical limits and populations at risk are expanding because of growing international markets, improved transportation systems, and demographic changes such as population movements. While many in developed countries will recognize meat-borne zoonoses such as trichinellosis and cysticercosis, far fewer are acquainted with the fish-borne parasitic zoonoses which are mostly helminthic diseases caused by trematodes, cestodes and nematodes. Yet these zoonoses are responsible for large numbers of human infections around the world. The list of potential fish-borne parasitic zoonoses is quite large. However, in this review, emphasis has been placed on liver fluke diseases such as clonorchiasis, opisthorchiasis and metorchiasis, as well as on intestinal trematodiasis (the heterophyids and echinostomes), anisakiasis (due to *Anisakis simplex* larvae), and diphyllobothriasis. The life cycles, distributions, epidemiology, clinical aspects, and, importantly, the research needed for improved risk assessments, clinical management and prevention and control of these important parasitic diseases are reviewed.

Keywords: Zoonoses; Parasite; Fish; Trematode; Cestode; Nematode

1. Introduction

Humans suffer from numerous parasitic foodborne zoonoses, many of which are caused by helminths. The helminth zoonoses of concern in this review are those transmitted from fish, freshwater, brackish and marine. In the past, these diseases were limited for the most part to populations living in low- and middle-income countries, but the geographical limits and populations at risk are expanding and changing because of growing international markets, improved transportation systems, and demographic changes (such as population movements). The World Health Organization (1995) has estimated that the number of people currently infected with fish-borne trematodes exceeds 18 million, but worldwide the number of people at risk, including those in developed countries, is more than half a billion. The recognition of the public health significance of these zoonoses, their links to poverty and cultural traditions, to intensification of agriculture, to environmental degradation, and the lack of tools for control is increasing (World Health Organization, 1995, 2004). This is due in no small measure to the process by which priorities in national public health systems are developed, which is usually a competitive exercise, and in which the justification for devoting greater attention and resources to fish-borne parasitic zoonoses is generally handicapped by the lack of good data on health and economic impacts. The genesis of this review was a desire to draw attention to the problem of these zoonoses and, hopefully, inspire greater efforts to acquire reliable global impact assessments and to develop a greater scientific basis for designing prevention and control programs. Compared with other well-studied parasitic diseases, fish-borne parasitic zoonoses have been public health orphans in the world of research funding, due in no

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small measure to insufficient appreciation of a crucial fact that most of them exist as a complex of parasite species whose transmission is often dependent on well-entrenched human behaviors. Because the modes of human infection are so similar, collectively these zoonoses may in many locations have a much greater aggregate effect than some other better-known parasitic diseases. The difficulties of diagnosis, the complexities of human cultural behaviors and the poor understanding of potential economic costs have made this field simultaneously daunting, scientifically obscure and, therefore, somewhat unattractive to investigators especially in developed countries. However, the challenge of developing a prevention and control strategy that accommodates strong cultural and agricultural traditions will test the imaginations and skills of researchers, an intellectual challenge that could provide the stimulation needed to build a more concerted international effort.

The list of potential fish-borne zoonoses that might be discussed in a review is quite large. While many in developed countries will recognize meat-borne zoonoses such as trichinellosis and cysticercosis, far fewer are acquainted with fish-borne parasitic zoonoses like opisthorchiasis, intestinal trematodiasis, anisakiasis or diphyllobothriasis. Yet these zoonoses are responsible for large numbers of human infections. We have chosen to focus on those that are considered currently the most significant (World Health Organization, 1995), but an effort is made to present references to many others that do occur in various regions. The emphasis is on basic biological and epidemiological features, and highlighting of knowledge gaps that need greater research investment and, ultimately, effective prevention and control strategies.

2. Trematodiases

2.1. The liver flukes

The liver flukes are a closely related group of trematodes belonging to the family Opisthorchiidae, and have similar life cycles and epidemiologies (Table 1). Liver flukes have long been known to cause serious disease in certain areas of the world. Cholangitis, choledocholithiasis, pancreatitis, and cholangiocarcinoma are the major clinical problems, associated with the long chronic pattern of these infections. Although the extent of the problem is difficult to assess due to the lack of comprehensive epidemiological studies, particularly in Southeast Asia, there is evidence that the greatest risk factor for humans, the consumption of raw or improperly cooked or processed fish, is increasing in some regions, facilitated partly by population migrations and partly by commercial provision of these products (World Health Organization, 2004). The causative agents of human infections include *Clonorchis sinensis* (Cobbold, 1875) Looss, 1907 (in East and Southeast Asia), *Opisthorchis viverrini* (Poirier, 1886) Stiles and Hassall, 1896 (in Southeast Asia), *Opisthorchis felineus* (Rivolta, 1884) Blanchard, 1895 (in Russia and Eastern Europe), and *Metorchis conjunctus* (Cobbold, 1860) Looss, 1899 (in North America) (Table 1). A total of 17 million people around the world are estimated to be infected with these liver flukes (World Health Organization, 1995).

2.1.1. Prevalence and distribution

Clonorchis sinensis, the Chinese liver fluke, is the most important species of fish-borne zoonotic parasite in East

Table 1
Species of liver flukes reported from humans

Species	Molluscan and piscine hosts	Other definitive hosts	Geographic distribution
Clonorchis sinensis	Freshwater snails[a] and fish[b]	Dogs, cats, rats, pigs, badgers, weasels, camels buffaloes	Korea, China, Taiwan, Vietnam, Russia
Opisthorchis viverrini	Freshwater snails[c] and fish[d]	Dogs, cats, rats, pigs	Thailand, Laos, Cambodia, Vietnam
Opisthorchis felineus	Freshwater snails[e] and fish[f]	Dogs, foxes, cats, rats, pigs, rabbits, seals, lions, wolverines, martens, polecats	Spain, Italy, Albania, Greece, France, Macedonia, Switzerland, Germany, Poland, Russia, Turkey, Caucasus
Metorchis conjunctus	Freshwater snails[g] and fish[h]	Dogs, cats, wolves, foxes, coyotes, raccoons, muskrats, minks, fishers	Canada, USA

[a] Species include *Parafossarulus manchouricus, Parrafossarulus anomalospiralis, Alocinma longicornis, Bithynia fuchsiana, Bithynia misella, Melanoides tuberculata, Semisulcospira libertina, Assiminea lutea,* and *Thiagra granifera* (Chen et al., 1994).

[b] *Species include Pseudorasbora parva, Abbottina (= Pseudogobio) rivularis, Ctenopharyngodon idellus, Carassius carassius, Carrassius auratus, Cultriculus (= Hemiculter)* spp., *Cyprinus carpio, Cyprinus carpio nudus, Opsariichthys spp., Rhodeus* spp., *Sarcocheilichthys* spp., *Zacco platypus, Zacco temminckii*, and *Hypomesus olidus*(Rim, 1982a; Chen et al., 1994; Park et al., 2004).

[c] Species include *Bithynia (siamensis) goniomphalus, Bithynia (siamensis) funiculata*, and *Bithynia (siamensis) siamensis* (Rim, 1982b).

[d] Species include *Cyclocheilichthys siaja, Hampala dispar, Puntius orphoides, Puntius gonionotus, Puntius proctozysron, Puntius viehoever, Labiobarbus lineatus, Esomus metallicus*, and *Osteochilus* sp. (Rim, 1982a; Kaewkes, 2003).

[e] Species include *Bithynia (Bulimus) leachi, Bithynia inflate,* and *Bithynia tentaculata* (Rim, 1982b).

[f] Species include *Idus melanotus, Tinca tinca, Tinca vu1garis, Abramis brama, Abramis sapa, Barbus barbus, C. carpio, Blicca bjorkna, Leuciscus idus, Alburnus lucidus, Aspius aspius*, and *Scardinius erythophthalmus* (Rim, 1982a).

[g] Species include *Amnicola limosa limosa* (MacLean et al., 1996).

[h] Species include *Catostomus catostomus, Salvelius fontinalis*, and *Perca flavescens* (MacLean et al., 1996).

Asia (Rim, 1990; Chen et al., 1994; Hong, 2003). It is widely distributed in this region (Table 1). In 1947, the estimated number of infected people worldwide was about 19 million (Stoll, 1947), but more recently it has been estimated to be about 7–10 million (World Health Organization, 1995; Crompton, 1999). In Japan, this parasite was formerly quite prevalent, but has been successfully controlled since the 1960 s (Chen et al., 1994; Hong, 2003). Current endemic areas of clonorchiasis include South Korea, China (except northwestern parts), Taiwan, northern Vietnam, and the far eastern part of Russia (Tables 1 and 2).

In the Republic of Korea, national surveys in 1971 and 2004 revealed 1.4–4.6% egg positive rates (Korea Association of Health Promotion, 2004); the number of infected people currently in Korea is estimated at about 1.5 million. In China, clonorchiasis is distributed in a total of 24 provinces, municipalities and autonomous regions (Chen et al., 1994). Guangdong Province (including Hong Kong) and Guangxi Zhuang Autonomous Region, Heilongjiang, Jilin and Liaoning provinces are the areas with most reported infections (Yu et al., 2003). In a nationwide survey, the prevalence of *C. sinensis* was 0.4% among almost 1.5 million people examined (Xu et al., 1995). Based on these data, the number of infected people in China may be about 6 million. In Hong Kong, the prevalence has decreased owing to control measures (Chen et al., 1994). In Taiwan, clonorchiasis was formerly endemic in three areas, Mei-Nung in the south, Sun-Moon Lake in the center and Miao-Li in the north (Cross, 1984), but the current status is unknown. In Vietnam, clonorchiasis has been endemic mainly in the north, especially along the Red River Delta including Haiphong and Hanoi (Rim, 1982a; De et al., 2003). In southern parts of Vietnam, *C. sinensis* is not reported, although opisthorchiasis is reported to be endemic (De et al., 2003). Cases of *C. sinensis* infection have been reported in the Amur River territory, the far eastern part of Russia (Chen et al., 1994).

Opisthorchis viverrini is a particularly serious liver fluke (Rim, 1982b; Kaewkes, 2003) and is highly prevalent in Southeast Asia (Table 2) including Thailand, Laos, Cambodia and south Vietnam; about 9 million people are estimated to be infected globally (Yossepowitch et al., 2004). In Thailand, it is widespread in the north and northeastern regions. The number of infected people in the northeastern region alone was estimated in the 1960 s to be over 3.5 million (Wykoff et al., 1965), and this figure seems to have changed little; the estimated number of infected people is currently about 6 million (Sripa et al., 2003). In Laos, the Mekong River basin is the most heavily infected area (Chai et al., 2005). In Vietnam, several southern provinces such as Phu Yen have reported infections, with prevalences above 10% (De et al., 2003).

Opisthorchis felineus was first described from a naturally infected cat and subsequently from a man in 1892 (Beaver et al., 1984); it is now recognized as a natural parasite of dogs, cats, foxes, and pigs in eastern and southeastern Europe and the Asiatic parts of Russia and common also in southern, central, and eastern Europe, Turkey and Siberia west of the Ob River, including Tomsk and Tyumen (Table 2) (Rim, 1982b). In 24 regions of the Ukraine, the number of human infections reported between 1952 and 1968 was 9340 (Rim, 1982b). The global incidence in 1947 for this parasite was estimated to be about 1.1 million (Stoll, 1947); the incidence

Table 2
Reports on the prevalence of the liver flukes

Species	Country	Area (population)	Prevalence	Reference
Clonorchis sinensis	Republic of Korea	Five major rivers	21.5%	Seo et al., 1981
	Republic of Korea	Nakdong River	45.5%	Seo et al., 1981
	Republic of Korea	General population	1.4-4.6%	KAHP[a]
	China	24 provinces	1-57%	Chen et al., 1994
	China	Nationwide	0.4%	Xu et al., 1995
	China	Korean minority	4.5%	Xu et al., 1995
	China	Mongolian minority	1.8%	Xu et al., 1995
	China	Guangxi Zhuang minority	0.96%	Xu et al., 1995
	China	Guangxi Zhuang minority	31.6%	Yu et al., 2003
	Vietnam	Haiphong and Hanoi	73%	Rim, 1982a
	Vietnam	Ninh Binh province	13.7-31.0%	De et al., 2003
Opisthorchis viverrini	Thailand	Northeastern regions	79%	Wykoff et al., 1965
	Thailand	Nationwide	9.4%	Sripa et al., 2003
	Laos	Mekong riversides	70.3%	Chai et al. (2005)
	Vietnam	Phu Yen province	15.2-36.9%	De et al., 2003
Opisthorchis felineus	Russia	Tomsk	$>6\%$	Rim, 1982b[b]
	Russia	Ob Riber basin	$>95\%$	Rim, 1982b[c]
	Russia	Tyumen	45%	World Health Organization, 1995
	Ukraine	Dnieper River basin	5-40%	Yossepowitch et al., 2004

[a] Korea Association of Health Promotion (2004).
[b] Data based on human autopsies in 1892.
[c] Data based on a survey in 1976.

appears not to have changed significantly and is now estimated to be about 1.6 million (Yossepowitch et al., 2004).

Metorchis conjunctus, the Canadian liver fluke, is a parasite of carnivorous mammals in Canada and USA (MacLean et al., 1996). Human infections with this fluke have occurred in Canada since 1946 (Yamaguti, 1958), particularly in aboriginal populations from Quebec to Saskatchewan, and the eastern coast of Greenland (MacLean et al., 1996; Behr et al., 1998) (Table 1).

2.1.2. Taxonomy, biology and life cycle

The zoonotic members of the Opisthorchiidae are quite similar in morphology, life cycles and modes of transmission, which present serious difficulties in specific diagnosis (see below). All share a similar epidemiological feature, the transmission to their final host through the latter's consumption of raw or insufficiently cooked infected fish (sometimes shrimp). This common thread also dictates similar prevention and control strategies (see Section 2.1.5).

Clonorchis sinensis. Adult flukes are flat, leaf-like, 8–15 mm long and 1.5–4 mm wide (Rim, 1990) and differ from *O. felineus* and *O. viverrini* in having branched testes. Typical for the family, they live in the biliary tract of humans and domestic animals and produce eggs, which pass out through the common bile duct and intestines. The eggs are ingested by freshwater snails, including *Parafossarulus manchouricus* as the major vector (Table 1). In the snail, the miracidia hatch in the intestine or rectum and penetrate the rectal wall to reach perirectal tissues and develop as sporocysts (Rim, 1982a). Rediae are formed within the sporocyst 14 days after egg ingestion. Cercariae develop within the rediae, and migrate to the intrahepatic lymph space of the snail to mature. A cercaria possesses two eye spots, and membranous keels on its ventral and dorsal surfaces of the tail, important diagnostic characters. The cercariae are very similar among the various species of opishthorchiids, but they can be differentiated to some degree on the basis of flame cell patterns and number of pairs of penetration glands (Kaewkes, 2003). A free swimming cercaria, probably attracted by movements of the fish, penetrates beneath the fish's scales, loses its tail, and encysts, chiefly in muscles, less frequently under the scales, fins or gills, and transforms into an encysted metacercaria.

The metacercaria is round or oval, measuring 0.13–0.14×0.09–0.10 mm (difficult to determine unless excysted). More than 100 species of freshwater fishes belonging to 13 families, especially the Cyprinidae, and three species of freshwater shrimp can serve as the second intermediate host (Rim, 1986; Chen et al., 1994; Park et al., 2004). The susceptibility of each species of fish, however, is variable, and the infection rate varies greatly between species of fish. In Korea, Japan, and China, *Pseudorasbora parva*, for example, is the most commonly infected fish (Rim, 1982a, 1986; Chen et al., 1994). The mode of transmission to the definitive host is through consumption of raw, undercooked, or improperly pickled or smoked infected fish. The range of the definitive host species is very broad, and includes man and domestic animals (Table 1). In the final host, the metacercariae excyst in the duodenum and migrate to the common bile duct by way of the Ampulla of Vater, and then to the extrahepatic and intrahepatic bile ducts. The metacercariae grow to the adult stage in about 4 weeks after infection (Rim, 1986).

Opisthorchis viverrini. Four species of *Opisthorchis*, *O.viverrini*, *O. felineus*, *Opisthorchis noverca* and *Opisthorchis guayaquilensis*, are known to infect humans, although the latter two appear to be rare. *Opisthorchis viverrini* can be distinguished from *O. felineus* in having deeper lobulation and a more posterior location of the testes (Kaewkes, 2003). Their morphology and life cycles are similar to that of *C. sinensis*. The adult fluke inhabits the bile duct, sometimes the gall bladder. It is flat, elongate, lanceolate, and 5.5–9.6 mm long and 0.8–1.7 mm wide (Rim, 1982b). The freshly passed eggs are eaten by freshwater snails of the genus Bithynia spp. (Table 1) in which the miracidia develop through the sporocysts, rediae, and cercariae stages. Free swimming cercariae penetrate the scale and skin of the fish, lose their tail, and encyst chiefly in muscles (Vichasri et al., 1982) and head of the fish (Tesana et al., 1985). The metacercaria is oval, and 0.20×0.17 mm in size. Various species of freshwater fish can serve as second intermediate hosts (Table 1) (Wykoff et al., 1965; Kaewkes, 2003). When ingested by a suitable definitive host (man, pigs, cats, dogs, rats), the metacercariae excyst in the duodenum, and migrate through the common bile duct to the intrahepatic bile ducts, where they mature in 3–4 weeks.

Opisthorchis felineus. The morphology of adult flukes is very similar to that of *O. viverrini* and *C. sinensis*. The eggs are slightly elongated ovoidal in shape, and very difficult to distinguish from other members of the family (Rim, 1982b). The life cycle and range of host species are very similar to that of *O. viverrini* (Table 1).

2.1.3. Epidemiology and factors related to emergence/re-emergence

All the zoonotic liver flukes share a common final transmission feature, i.e. ingestion of infected fish, their overall epidemiological features are very similar, and that of *C. sinensis* is illustrative. The presence of the snail, fish and mammalian hosts (including man) is essential to transmission, and this combination must be sustainable for the parasite to remain endemic in a region (Tables 1–3). Because the availability of susceptible snail species is crucial, the geographical distribution of liver flukes, particularly *C. sinensis*, closely parallels the distribution of particular snail host species. Although the prevalence of infection in a snail population can be as low as 0.08%, even

Table 3
Important heterophyid species reported from humans

Species	Molluscan and piscine hosts	Other definitive hosts	Geographic distribution
Metagonimus yokogawai	Freshwater snails[a] and fish[b]	Dogs, cats, rats	Korea, China, Taiwan, Japan, Russia, Indonesia, Israel, Spain
Metagonimus takahashii	Freshwater snails[c] and fish[d]	(experimentally) mice, dogs	Korea, Japan
Metagonimus miyatai	Freshwater snails[e] and fish[f]	(experimentally) mice, rats, hamsters, dogs	Korea, Japan
Heterophyes heterophyes	Brackish water snails[g] and fish[h]	Cats, dogs, foxes, wolves pelicans	Egypt, Sudan, Palestine, Brazil, Spain, Turkey, Iran, India, Russia
Heterophyes nocens	Brackish water snails[i] and fish[j]	Cats	Korea, Japan, China
Haplorchis taichui	Freshwater snails[k] and fish[l]	Cats, dogs, foxes egret	Taiwan, Philippines, Bangladesh, India, Palestine, Egypt, Malaysia, Thailand, Laos, Vietnam, China
Haplorchis pumilio	Freshwater snails[m] and fish[n]	Cats, dogs, foxes, wolves pelicans	Thailand, Laos, China
Haplorchis yokogawai	Freshwater snails[o] and fish[p]	Cats, dogs, egret	Taiwan, Philippines, China, Malaysia, Indonesia, Thailand, Laos, India, Australia, Egypt
Pygidiopsis summa	Brackish water snails[q] and fish[r]	Cats	Korea, Japan

Other minor fish-borne heterophyids reported from man include *Centrocestus armatus, Centrocestus cuspidatus, Centrocestus caninus, Centrocestus kurokawai, Centrocestus longus, Heterophyopsis continua, Stellantchasmus falcatus, Stictodora fuscata, Stictodora lari, Procerovum calderoni, Procerovum varium, Phagicola* sp., *Appophalus donicus*, and *Cryptocotyle lingua* (Yu and Mott, 1994; Chai and Lee, 2002).

[a] Species include *Semisulcospira libertina* or *Semisulcospira coreana* (Chai and Lee, 2002).

[b] Species include *Plecoglossus altivelis, Tribolodon* sp., and *Lateolabrax japonicus* (Chai and Lee, 2002).

[c] Species include *S. coreana* or *Koreanomelania nodifila* (Chai and Lee, 2002).

[d] Species include *Carassius carassius, Cyprinus carpio*, and *Tribolodon taczanowskii* (Chai and Lee, 2002).

[e] Species include *Semisulcospira globus* (Chai and Lee, 2002).

[f] Species include *Zacco platypus, Zacco temmincki, P. altivelis, Tribolodon* sp., and *Morocco steindachneri* (Saito et al., 1997).

[g] Species include *Pirenella conica* (Taraschewski, 1984, PhD Dissertation to Universitat Hohenheim, Germany).

[h] Species include *Mugil cephalus, Tilapia nilotica, Aphanius fasciatus,* and *Acanthogobius* sp. (Yu and Mott, 1994).

[i] Species include *Cerithidea cingulata* (= *Tympanotonus microptera*) (Chai and Lee, 2002).

[j] Species include *M. cephalus* and *Acanthogobius flavimanus* (Chai and Lee, 2002).

[k] Species include *Melania reiniana* var. *hitachiens* (Velasquez, 1982).

[l] Species include *C. carpio, C. auratus, Z. platypus, Pseudorasbora parva, Rodeus ocellatus, Gambusia affinis, Ctenopharyngodon idellus, Puntius orphoides, Puntius leicanthus, Puntius gonionotus, Puntius binotatus,* and *Puntius palata* (Velasquez, 1982).

[m] Species include *Melania obliquegranosa, Melania juncea,* or *Melanoides tuberculata* (Faust and Nishigori, 1926; Velasquez, 1982).

[n] Species include *M. cephalus, Mugil capito, Ophicephalus striatus, Glossogobius giurus, Therapon plumbeus, Gerris filamentosus, Teuthis javus, Ambassis buruensis, Astatotilapia desfontainesi, Acanthogobius* sp., *Anabas* sp., *Carrasius* sp., *Cyprinus* sp., *Tilapia simonies, Tilapia galilea, Tilapia nilotica, Barbus canis, Barbus longiceps*, and *P. binotatus* (Velasquez, 1982).

[o] Species include *M. tuberculata* or *Stenomelania newcombi* (Velasquez, 1982).

[p] Species include *Mugil* spp., *Puntius* spp., *Misgurnus* sp., *Gerris kapas, A. buruensis, Amphacanthus javus, Hemiramphus georgii*, and *O. striatus* (Velasquez, 1982).

[q] Species include *Cerithidea* (= *Tympanotonus*) sp. (Chai and Lee, 2002).

[r] Species include *M. cephalus* and *A. flavimanus* (Chai and Lee, 2002).

in highly endemic areas, this is sufficient to maintain the life cycle because snails infected with *C. sinensis* may release an average of 788 cercariae per snail daily, with a maximum 5840 cercariae per snail (Rim et al., 1982a). In addition, the shedding interval during the year may be long; in Korea, cercarial shedding has been observed to extend from May to October (Rim, 1982a). This aspect of the epidemiology of *O. viverrini* is similar and although snail infection rates may also be quite low (0.083–1.6%), this level is sufficient to maintain endemicity (Kaewkes, 2003). In contrast, both the prevalence and intensity of infection of the fish hosts with metacercariae can be very high (Guoqing et al., 2001; Sukontason et al., 2001b). Often 94–100% of fish examined can be infected with zoonotic metacercariae (Vichasri et al., 1982; Ooi et al., 1997).

The prevalence of liver flukes in endemic areas is, of course, related to the human custom of eating raw fish or shrimps. The morning congee (rice gruel) with slices of raw freshwater fish (southern China and Hong Kong) or slices of raw freshwater fish with red pepper sauce (Korea) are examples of major dietary sources of *C. sinensis* infection; half roasted or undercooked fish in Guangdong Province and raw shrimps in Fujian Province are other dishes commonly involved in China (Chen et al., 1994). In northeastern Thailand and Laos, it is well established that ‘Koi pla’, the most popular raw fish dish, particularly among Thai of Lao descent, is an important food source of infection with *O. viverrini*. The ‘Koi pla’ dish consists of raw fish flesh chopped with garlic, lemon juice, fish sauce, chili, roasted ground rice, and local vegetables (Rim, 1982b). Other similar dishes include ‘Pla ra’, ‘Pla som’, ‘Pla lap’, ‘Som fak’ and ‘Pla kaw’.

Associated with the habit of eating raw fish, characteristic patterns of age and sex prevalence are known among residents of clonorchiasis endemic areas. The rates are generally higher in men than in women, and higher in adults than in children (Rim, 1982a; De et al., 2003). For example, men 25–55 years old and women over 45 years are the most highly affected groups in Guangxi Province, China (Chen et al., 1994) and Vietnam (De et al., 2003). This reflects most likely the behavior pattern of men, who more often gather together for dinners of raw or pickled fish (usually accompanied by alcohol) than to any biochemical or physiological differences between genders. As with *C. sinensis*, the infection pattern of *O. viverrini* indicates that initial infections in people occur at a very young age and rise rapidly with age, remaining relatively high throughout life (Upatham and Viyanant, 2003). However, in contrast to *C. sinensis*, no significant differences are generally seen between men and women in the infection rates of *O. viverrini*. One factor may be that in Thailand, mothers frequently feed raw or partly cooked fish to infants, and this may explain the lack of gender differences, along with the widespread popularity of food dishes such as 'Koi pla' (Sithithaworn and Haswell-Elkins, 2003).

The role of reservoir hosts, especially cats, dogs, and pigs (Table 1), in maintaining liver fluke endemicity has not been well-studied (Chen et al., 1994; World Health Organization, 1995; Sithithaworn and Haswell-Elkins, 2003), and there is a lack of consensus on their importance in transmission risk to humans (Rim, 1986; World Health Organization, 1995; Mas-Coma and Bargues, 1997; De et al., 2003; Sithithaworn and Haswell-Elkins, 2003). In some areas, infection may be high among people and low among domestic animals and vice versa (China), but in other endemic areas, these reservoir hosts may also have infection rates comparable with that in humans (World Health Organization, 1995; Mas-Coma and Bargues, 1997; De et al., 2003). This is not a trivial issue because the role of reservoir hosts may have an important bearing on the outcome of mass drug treatment control programs (see Section 2.1.5). If mass drug treatment is targeted only to humans (World Health Organization, 2004), will infected domestic animals represent a significant risk reservoir for reestablishing transmission to former levels in humans?

The transmission of *O. viverrini* cercariae is often seasonal particularly where changes in rainfall and temperature are marked. In Thailand, e.g. peak local contamination of local water bodies, and associated snail infections, occurs at the height of the rainy season when surface human and animal fecal contamination and household effluents are washed into ponds, streams and lakes (Sithithaworn and Haswell-Elkins, 2003). Consequently, transmission of *O. viverrini* to fish, and subsequently humans, may be highest just after the peak of monsoon flooding when intermediate hosts are abundant (Vichasri et al., 1982).

This has prompted strategic control designs that attempt to exploit this seasonal variability by intervening in the transmission cycle when the parasite transmission and abundance are at its lowest and most vulnerable level (see Section 2.1.5). Seasonal effects on the transmission of *C. sinensis* are also known; cercarial transmission occurs from May to October in Korea, and between March and October in Taiwan, a more southerly latitude (Mas-Coma and Bargues, 1997). Temperature is the primary determinant and manifests its effect in regulation of snail development (Japan) and/or directly on the parasite's intra-snail stages (Korea) (Rim, 1982a).

An important feature in the epidemiology of human clonorchiasis is the role in transmission of less commonly infected fish species such as *Cyprinus carpio*, *C. carpio nudus,* and *Carassius auratus* (Tables 1 and 2). Although the metacercarial burdens of these large carp are generally very low, they are a preferred source of raw fish for people. In contrast, the most commonly infected small fish such as *P. parva*, which often have high metacercarial burdens, are much less preferred raw, particularly in Korea (Rim, 1982a; Mas-Coma and Bargues, 1997). This contributes to the pattern of accumulating infections by small numbers of metacercariae over a long period (20–30 years) (Rim, 1982a). This long-term accumulation of worm numbers suggests that humans, at least, do not acquire a significant level of immunity to reinfection. However, this is an area of neglect in liver fluke diseases, and more research is needed to understand the immunology of these infections in both humans and important domestic animal hosts.

The future impact of these fish-borne zoonotic parasites may be linked closely to the expected growth of aquaculture in Asia, where nearly 90% of freshwater production is centered (World Health Organization, 2004). However, in reviewing a large number of past studies on the epidemiology of these fish-borne trematodes, it is clear that there is disagreement on the relative importance of pond cultured fish versus wild caught fish in the epidemiology of human infection (see for example, World Health Organization, 1994a). Several food safety risk analyses of Asian aquaculture have reported (Naegel, 1990; Lima dos Santos, 1994, Proc. 37th Ann Conf Canadian Food Sci Technol, Vancouver, BC) that there are as yet no conclusive epidemiological studies that link the transmission of liver fluke infections to aquaculture, although in some countries, especially China where most of its fish are produced through pond culture, the high rates of *C. sinensis* infection are difficult to account for by consumption of wild fish alone. This is a crucial question, for both prevention and control planning, and for the expansion of fish farming in Asia, and deserves a higher research priority in the endemic countries. One such effort is now underway in Vietnam, called the FIBOZOPA Project (www.fibozopa.ria1.org).

Overall, the epidemiology of *O. felineus* is similar to that of the other liver flukes. Man and alternate hosts are infected by consumption of raw or insufficiently cooked or processed fish; in this zoonosis, consumption of even poorly prepared dried fish or fish pickled in garlic juice are potential sources of infection. A recent report described an outbreak of acute opisthorchiasis in a Western European family who ate raw fish exported from Siberia, attesting to the hardiness of the metacercariae and the risk in uninspected fish exports (Yossepowitch et al., 2004).

The definitive hosts of *M. conjunctus* other than humans include the wolf, fox, and dog (Table 1). Infections have caused death of sled dogs in Central Canada; necropsies indicated that the cause of death was liver damage associated with this fluke infection. This parasite is an example of emerging fish-borne parasitic zoonosis. Clinical details of acute infections in 19 Korean immigrants in Canada were described by MacLean et al. (1996). The victims ate wild-caught fish (*Catostomus catostomus*) prepared in insufficiently cooked but traditional dishes, not realizing that *M. conjuctus* was endemic in fish in the area.

2.1.4. Immigration: special risk issues

Immigration and similar demographic changes may be associated with new patterns of infection. There are several reports of Asian immigrants in North America with chronic infections of *Clonorchis/Opisthorchis*, especially among refugees from Southeast Asia (Sun, 1980; Arfaa, 1981; Lerman et al., 1982; Dao et al., 1984; Schwartz, 1986). Although this pattern will probably not lead to establishment of these parasites in North America because of lack of suitable snail intermediate hosts (although this has not been confirmed because of accidental introductions of Asian species of snails especially in Florida), they do present challenges to clinicians unfamiliar with the parasites, their diagnosis, and appropriate treatment. The risks associated with immigration are not limited to diagnosis and treatment of immigrants, however, e.g. a large number of imported Thai construction work laborers in Taiwan were infected with *O. viverrini*, which is not endemic to that country (Peng et al., 1993). This raises not only both the problem of diagnosis and treatment for local public health agencies, but also the need to assess the risk of establishing a new parasite through infection of natïve snail species. An interesting variation on the potential risks associated with the immigration is the recent report of Yossepowitch et al. (2004) of *O. felineus* infections in a family of Russian immigrants residing in Israel; a member of the family brought back from a visit to the family's former home in an endemic area of Siberia an infected fish, which was then consumed locally. This is a pattern that may become more frequent because of both population movements and increasing international travel.

2.1.5. Disease and public health impact

Diagnosis of liver fluke infections can be made by the recovery of eggs from feces by cellophane thick smear (Chai et al., 1982) or Kato-Katz techniques (Hong et al., 2003). However, the eggs must be differentiated from those of heterophyids and from various other opisthorchiid species, a task which requires considerable training and experience, and even then the lack of specific diagnostic tools such as molecular probes presents a challenge (Lee et al., 1984; Ditrich et al., 1992). Serological tests such as enzyme-linked immunosorbent assay (ELISA) using excretory-secretory antigens are helpful in some cases (Choi et al., 2003). There is interest in developing specific molecular or immunological methods to aid this task, but such methods have not yet appeared or gained acceptance (Wongratanacheewin et al., 2003). However, progress in this area is encouraging, for example, a PCR-based technique to detect snail and fish infections with *O. viverrini*, often a difficult task, has been reported (Maleewong et al., 2003). There are a number of gene sequences now published in GenBank, which should spur development of needed diagnostic tools.

The hepatic lesions and clinical manifestations in infected people are similar for all the liver fluke infections (Rim, 1982b; Beaver et al., 1984). Bronchial asthma and allergic lesions are encountered in early stages, along with painful enlargement of the liver, congestion of the spleen, and local eosinophilia in the wall of bile ducts in chronic and severe infections. Bile stones may form around eggs and cause cholecystitis and colicky pain. Carcinoma of the bile duct or the pancreas, with metastases into the epigastric lymph nodes, is responsible for death of some patients.

The adult worms of *C. sinensis* and *O. viverrini* are found commonly in the intrahepatic bile duct, some in the gall bladder and along the biliary tract of infected humans. The main pathogenesis in the biliary tract is mechanical, chemical, and immunological irritation by the worms (Li et al., 2004). This results in obstruction of the bile duct and bile stasis, periductal inflammation, and cholangitis. Histopathologically, enlargement of the bile duct, periductal fibrosis, adenomatous hyperplasia, and cystic degeneration are the most prominent features (Lee et al., 1978). In mild infections with less than 100 worms, the infection is usually asymptomatic. Several hundred to thousands of worms, however, can cause significant symptoms causing the patient to seek medication. Jaundice, indigestion, epigastric discomfort, anorexia, general malaise, diarrhea and mild fever are common clinical symptoms (Rim, 1990).

Complications such as pyogenic cholangitis, biliary calculi, cholecystitis, liver cirrhosis, pancreatitis and cholangiocarcinoma, are often associated with infection (Sripa, 2003). Among these, cholangiocarcinoma is the most serious (Watanapa and Watanapa, 2002; World Health Organization, 2004). It arises from metaplastic changes of biliary epithelial cells and usually occurs in the secondary intrahepatic bile ducts, where the flukes are preferentially situated (Chen et al., 1994). The contributing factors promoting carcinogenesis include ingestion of carcinogens or co-carcinogens, and host endogenous influences such as malnutrition, immunological defects, and genetic factors (Chen et al., 1994; World Health Organziation, 1994b).

However, the exact mechanisms of carcinogenesis are not clearly elucidated.

The severity of the pathology is associated with both intensity and duration of infection and the location of the lesions (Rim, 1982b). The histopathological changes include adenomatous hyperplasia of the biliary epithelium, thickening of the bile duct wall, periductal inflammation with eosinophils and round cells, and fibrosis in the portal areas. A large number of flukes can cause obstruction of the biliary tract. Based on 70 necropsy cases in Thailand, hepatomegaly was remarkable in most chronic and severe cases of opisthorchiasis, with marked dilatation and hypertrophy of the bile ducts (Sripa, 2003). Inflammation of the bile duct and cell infiltrations may be secondary to superimposed bacterial infections; suppurative cholangitis is frequently the end result and the infection may extend into the liver parenchyma causing hepatitis. Adenomatous and fibrous hyperplasia, seen in the bile ducts, can also occur in the pancreatic duct.

Moderate infection levels with less than 100 worms of *O. viverrini* are usually asymptomatic. However, infections with hundreds or thousands of worms can cause right upper quadrant pain, diarrhea, flatulence, fatigue, dyspepsia, pain over the liver, jaundice in some patients and a moderate elevation of the body temperature (Mairiang and Mairiang, 2003). High incidences of cholangiocarcinoma, based on both necropsy and liver biopsy data, have been reported for *O. viverrini*. For instance, in Khon Kaen, northeastern Thailand, the incidence of cholangiocarcinoma is estimated to be 129 per 100,000 males and 89 per 100,000 for females, compared with one to two per 100,000 in western countries (Vatanasapt et al., 1990). Jaundice usually occurs in cases with heavy infections and especially when there is carcinomatous transformation with an increased biliary obstruction. Patients with cholangiocarcinoma may present obstructive jaundice, fever, and acute complications such as cholangitis, acalculous cholecystitis and generalized bile peritonitis (Mairiang and Mairiang, 2003). Using hamsters as an experimental animal model, it was shown that chemical carcinogens such as dimethynitrosamine which is present in fermented fish including ‘Pla ra’ plays the role of an ‘initiator’, and *O. viverrini* acts as a ‘promoter’ for the development of cholangiocarcinoma (Thamavit et al., 1994).

2.1.6. Strategies for prevention and control

Prevention and control approaches are similar for all the liver flukes. The traditional human habit of eating raw or improperly cooked freshwater fish is a major reason for sustaining the zoonosis in endemic areas and a seemingly intractable obstacle to control; health education efforts aimed at changing such habits have not been very successful (Guoqing et al., 2001; World Health Organization, 2004). Currently, the major strategies for community prevention and control include fecal examination and treatment of individual cases with praziquantel (25 mg/kg, three times daily, for 2–3 days), health education to instill the need to consume only cooked fish, and environmental sanitation through the building and use of latrines in endemic areas. More recently, World Health Organization (2004) has recommended mass chemotherapy of people at risk in endemic areas as the most practical and immediately effective control strategy. Mass chemotherapy with praziquantel (40 mg/kg in a single dose) is highly efficient and generally feasible to distribute (Lee, 1984). Until more such control programs are implemented, however, and followed over time, the long-term effectiveness of this approach may be problematic.

Efforts to interrupt transmission at the intermediate host level apparently have not been extensive to date, judging by published reports. Several projects have been conducted on pond fish production in China, utilizing snail control and drug treatment of infected members of the household, along with intensive health education of the community on the risks of eating raw fish. The effect on transmission over 2 years was mixed, however, with a decline in prevalence in people, but only a modest impact on snail populations, on the use of human feces as pond fertilizer and on the habit of eating raw fish (Guoqing et al., 2001). In Thailand, a FAO-led HAACP approach to fish pond management was carried out that focused on water supply, fish fry, fish feed and pond conditions to eliminate contamination of the ponds with *O. viverrini* eggs and snail infections. A preliminary report indicated some success with this intensive effort, but a full assessment of its sustainability over a period of years is needed (Khamboonraung et al., 1997). Irradiation of fish to control infectivity of metacercariae was tried for *C. sinensis* (Lee et al., 1989) and *O. viverrini* (Sornmani et al., 1993); however, feasibility of the method economically, and consumer acceptance appear to be obstacles to the use of this prevention method.

2.2. The intestinal flukes—heterophyids

These minute intestinal flukes of the family Heterophyidae are parasites of birds and mammals (Table 3). A large number of species have been reported from humans, among which *Metagonimus yokogawai* and *Heterophyes heterophyes* are generally considered the most important species (Yu and Mott, 1994). However, because an extraordinary number of heterophyid species are zoonotic (about 35 species) and have very similar transmission patterns, this group is in the aggregate a very significant food safety and quality problem, but one has not attracted the interest of international agencies until recently. The importance of these flukes is being increasingly recognized through recent studies from the Philippines (Belizario et al., 2001), from Thailand on *Haplorchis taichui* (Waikagul, 1991; Sukontason et al., 2001a) and from Korea on several species including *Heterophyes nocens* and *Metagonimus* spp. (Chai and Lee, 1991, 2002).

Although generally not considered of significant clinical importance relative to the liver flukes, several heterophyid species, including *Stellantchasmus falcatus*, *Haplorchis* spp., and *Procerovum* spp., can cause significant pathology, often fatal, in the heart, brain, and spinal cord of humans (Africa et al., 1940; World Health Organization, 1995). The exact mechanisms of pathogenesis responsible are not clear but may be related to invasion of the circulatory system by worm eggs. Disease is usually related to worm burdens, which in some cases can be very heavy (MacLean et al., 1999).

Another very important issue related to heterophyids is the difficulty of differentiating the eggs from those of the liver flukes in human fecal examinations, which may cause inaccurate estimates of the prevalences of both trematode groups (Lee et al., 1984; Chai and Lee, 1991, 2002; Ditrich et al., 1992). New diagnostic techniques including PCR are needed to improve specific diagnosis of these flukes. The discussion which follows focuses on the more common of these intestinal flukes, and refers in Table 3 to the other less frequently encountered species. Each species is discussed separately because of individual variation, but it should be noted that it is more common to encounter multiple species infections rather than infections with single species, which compounds the problem of diagnosis by fecal examinations (Lee et al., 1984; Giboda et al., 1991; Ditrich et al., 1992).

2.2.1. *Metagonimus yokogawai (Katsurada, 1912) Katsurada, 1912*

The genus *Metagonimus* is characterized by a laterally deviated ventral sucker and absence of ventrogenital apparatus or genital sucker (Chai and Lee, 2002). Four species, namely *M. yokogawai*, *Metagonimus takahashii, Metagonimus minutus*, and *Metagonimus miyatai*, have been reported from humans (Table 3). Adult flukes of *M. yokogawai* are 1–2 mm long and 0.4–0.6 mm wide, and characterized by the presence of two closely adjacent testes. The molluscan intermediate host is a fresh water snail (Chai and Lee, 2002). The species has rather broad fish host specificity, but the most important fish host in the Republic of Korea and Japan is sweetfish *Plecoglossus altivelis* (Table 3). In the Republic of Korea, almost all large and small streams in eastern and southern coastal areas are endemic foci, with 10–70% egg positive rates among residents (Chai et al., 1977; Seo et al., 1981; Chai and Lee, 2002). Human infections have also been recorded from Siberia, Europe, China, and Taiwan (Yu and Mott, 1994). In Japan, the prevalence has decreased since the 1970 s, except in a few foci such as areas surrounding the Hamana Lake (Ito et al., 1991). In Russia, *M. yokogawai* is endemic in the Amur and Ussuri valleys of Khabarovsk territory, where the prevalence in ethnic minority groups varies between 20 and 70% (Yu and Mott, 1994).

The adult flukes parasitize the mucosa of the middle part of the small intestine (Chai, 1979). Intestinal histopathology is characterized by villous atrophy and crypt hyperplasia, with variable degrees of inflammatory reactions (Chai, 1979). In light infections, fatigue and mild gastrointestinal troubles such as epigastric pain, diarrhea and anorexia are present; in heavy infections, abdominal cramps, malabsorption and weight loss may occur. The diagnosis is made by recovery of the eggs in fecal examinations.

Control measures include treatment of infected people, environmental sanitation, and health education. The drug of choice is praziquantel; the efficacy of a single oral dose of 10–20 mg/kg is satisfactory (Chai and Lee, 2002). Irradiation of the sweetfish by 200 Gy is highly effective in controlling infectivity of metacercariae (Chai et al., 1995). The infection can be prevented by the avoidance of eating uncooked fresh water fish.

2.2.2. *Other Metagonimus spp. infecting humans*

Metagonimus takahashii Suzuki, 1930 was reported in Japan from mice and dogs fed with metacercariae encysted in fresh water fish other than sweetfish (Chai and Lee, 2002). *Metagonimus miyatai* Saito et al., 1997 was first found in Japan in 1941, but its taxonomic significance was later established to be a distinct species (Saito et al., 1997). These two species (Table 3) are morphologically distinguished from *M. yokogawai* in the position of the two testes, the distribution of vitelline follicles, and the larger egg sizes (Saito et al., 1997; Chai and Lee, 2002). The three species are also distinguished genetically by PCR based-restriction fragment length polymorphism (PCR-RFLP) patterns, karyotypes, simple sequence repeat-PCR (SSR-PCR) patterns (Chai and Lee, 2002), and sequences of 28S ribosomal DNA and mitochondrial cytochrome c oxidase subunit I (Lee et al., 2004). In the Republic of Korea, adult flukes of both species have been confirmed in inhabitants along the Namhan River (Chai et al., 1993). The prevalence of *M. miyatai* infection was also reported along the Gum River, Daechong Reservoir, Hantaan River, and Nakdong River (Chai and Lee, 2002).

2.2.3. *Heterophyes heterophyes (v. Siebold, 1852) Stiles and Hassall, 1900*

The genus *Heterophyes* is characterized by the median location of the ventral sucker and the presence of a genital sucker armed with gonotyl (Chai and Lee, 2002). Three species, namely *H. heterophyes*, *Heterophyes dispar* and *H. nocens* (syn. *Heterophyes katsuradai*), are responsible for human infections (Yu and Mott, 1994; Chai et al., 1986; Chai and Lee, 2002). *Heterophyes heterophyes* was discovered in 1851 at autopsy of an Egyptian in Cairo, and is now known to be distributed in many parts of the world (Tarashewski, 1984, PhD Thesis, Universitat Hohenheim, Germany; Yu and Mott, 1994) (Table 3). Adult flukes are minute, 1.0–1.7 mm long, 0.3–0.4 mm wide, and characterized by the presence of a large, median ventral sucker and a genital sucker with gonotyl armed with 60–90 multidigitate spines (Beaver et al., 1984). The eggs are similar to many other heterophyid and opisthorchiid species. The snail and fish hosts are brackish water species (Table 3).

In Egypt, human infections are prevalent among the inhabitants of the northern part of the Nile Delta, where fishermen and domestic animals frequently consume fish, including mullet *Mugil cephalus* (Yu and Mott, 1994). During 1987–1991, the prevalence of heterophyiasis in five Governorates of the Nile Delta ranged between 0.01 and 1%. A review of 299 human cases in Dakahlia Governorate indicated that the disease is common in both urban and rural localities owing to the habit of consuming salted or insufficiently baked fish (Yu and Mott, 1994). The metacercariae can survive up to 7 days in salted fish (Yu and Mott, 1994). The mean prevalence of heterophyid infections in the villages of Khuzestan, southwest Iran, was found to be 8% (2–24% in range). In postmortem examination of carnivores in the same areas, 14.2% of jackals, 33.3% of foxes, and 2.5% of dogs were infected with *H. heterophyes* and *M. yokogawai* (Massoud et al., 1981). Human infections were also reported in Japan (Kagei et al., 1980) and the Republic of Korea (Chai et al., 1986; Chai and Lee, 2002); however, these cases were imported from Egypt to Japan and from Saudi Arabia and Sudan to Korea.

2.2.4. *Heterophyes nocens* Onji and Nishio, 1916

Heterophyes nocens Onji and Nishio, 1916 (syn. *H. katsuradai* Ozaki and Asada, 1926) was first reported in Japan from experimental dogs and cats fed with metacercariae from the mullet *M. cephalus*, and it is now known to occur elsewhere in the Far East (Chai and Lee, 2002) (Table 3). This species is distinguished from *H. heterophyes* by the smaller number (50–62) of spines on the gonotyl. The snail and fish hosts are brackish water species. In the Republic of Korea, before 1989, only 13 human cases were detected (Chai and Lee, 2002). In April 1990, however, a highly endemic focus was discovered on a southwestern coastal island, where 42 (43%) of 98 residents examined were infected (Chai et al., 1994a). Another endemic area with a prevalence of 75% was later found in a western coastal village (Chai et al., 1997). Several other coastal areas and many islands have been added to the list of endemic areas (Chai and Lee, 2002; Chai et al., 2004). In Japan, human *H. nocens* infections were reported from Kochi, Chiba, Yamaguchi, Chugoku and Hiroshima Prefectures (Suzuki et al., 1982). Recently, two lakeside villages of Mikkabi-cho, at the north end of Hamana Lake, Shizuoka Prefecture, were found to have prevalences of 7.5 and 10.5% (Kino et al., 2002a, b).

2.2.5. *Haplorchis* spp.

The genus *Haplorchis* is characterized by the presence of only one testis and a ventro-genital-sucker complex armed with gonotyl and chitinous spines (Yamaguti, 1958). Five species, namely *H. taichui, Haplorchis pumilio*, *Haplorchis yokogawai*, *Haplorchis pleurolophocerca*, and *Haplorchis vanissimus*, are responsible for human infections (Yu and Mott, 1994); the first three are the most important (Table 3). *Haplorchis taichui* (Nishigori, 1924) Chen, 1936 was first described from birds and mammals from central Taiwan (Faust and Nishigori, 1926). Human infections are now commonly found throughout Asia (Velasquez, 1982). *Haplorchis pumilio* (Looss, 1986) was originally described from birds and mammals in Egypt; it is also now known to be distributed in Asia (Velasquez, 1982; Yu and Mott, 1994). *Haplorchis yokogawai* (Katsuta, 1932) was described from dogs and cats fed with metacercariae from mullet in Taiwan; human infections have now been reported from many Asian countries, Australia, and Egypt (Velasquez, 1982; Yu and Mott, 1994).

2.3. *The intestinal flukes—echinostomes*

Trematodes of the family Echinostomatidae (Poche, 1926) are intestinal parasites of birds and mammals. At least 30 genera and more than 200 species are known; about 15 species infect humans (Yamashita, 1964; Huffman and Fried, 1990). There are 11 reported fish-borne echinostome species (Table 4) of which *Echinostoma hortense* and *Echinochasmus japonicus* are the most important (Yu and Mott, 1994; Chai and Lee, 2002). Most human echinostome infections have been reported from Asia and the Western Pacific, but infections probably occur also in Africa (Yu and Mott, 1994). The disease is generally mild, but ulcerations and bleeding in the stomach or duodenum may occur, as in *E. hortense* infection (Chai et al., 1994b).

2.3.1. *Echinostoma hortense* Asada, 1926

The genus *Echinostoma* Rudolphi, 1809 is characterized by an elongated body and presence of a head collar with dorsally uninterrupted crown of spines (Yamaguti, 1958). More than 95 species are known (Yamaguti, 1958), and seven species infect humans (Yamashita, 1964; Yu and Mott, 1994). *Echinostoma hortense* has 27 or 28 collar spines around the oral sucker, and two tandem and slightly lobulated testes. It was first described from synanthropic rats in Japan, and then from humans and rodents in the Republic of Korea (Chai and Lee, 2002) and China (Yu and Mott, 1994) (Table 4). An infection rate of 22.4% has been reported among residents of Cheongsong-gun, Republic of Korea (Chai and Lee, 2002). In a survey in Liaoning province, northeast China, 6 of 10 hospitalized hepatitis patients who had eaten raw loach were found infected, and 69.7% of loach, *Misgurnus anguillicaudatus*, examined from a local market were infected (Yu and Mott, 1994).

In experimental rats, infection produces villous atrophy, crypt hyperplasia, inflammation of the stroma, and decreased villus/crypt ratios (Chai and Lee, 2002). Mucosal damage is generally more severe than in heterophyid infections. Abdominal pain, diarrhea, and fatigue are the major symptoms. Chai et al. (1994b) reported that a patient with *E. hortense* infection suffered from severe ulcerative lesions and bleeding in the duodenum. Specific diagnosis can be made through careful observations and measurements of the eggs. Treatment with 10–20 mg/kg praziquantel in a single oral regimen is effective (Chai and Lee, 2002).

Table 4
Important fish-borne echinostome species reported from humans

Species	Piscine hosts	Other definitive hosts	Geographic distribution
Echinostoma hortense	Freshwater snail[a] and fish[b]	Rats, dogs, cats, mice	Korea, Japan, China
Echinochasmus japonicus	Freshwater snail[c] and fish[d]	Chickens, ducks	Korea, Japan, China
Echinochasmus perfoliatus	Freshwater snail[e] and fish[f]	Foxes, rats, wild boars, dogs	Japan, China, Taiwan, Hungary, Italy, Rumania, Russia
Echinochasmus liliputanus	Freshwater snail[g] and fish[h]	Dogs, cats, badgers, foxes, raccoons	Egypt, Syria, Palestine, China
Echinochasmus fujianensis	Freshwater snail[i] and fish[j]	Dogs, cats, pigs, rats	China

Other minor fish-borne echinostomes reported from man include *Echinostoma cinetorchis, Echinostoma angustitestis,* and *Episthmium caninum* (Yu and Mott, 1994; Chai and Lee, 2002).

[a] Species include *Lymnaea pervia* and *Radix auricularia coreana* (Chai and Lee, 2002).

[b] Species include *Misgurnus anguillicaudatus, Misgurnus mizolepis, Odontobutis obscura interrupta, Moroco oxycephalus, Coreoperca kawamebari,* and *Squalidus coreanus* (Chai and Lee, 2002).

[c] Species include *Parafossarulus manchouricus* (Chai and Lee, 2002).

[d] Species include *Pseudorasbora parva, Hypomesus olidus,* and *Gnathopogon strigatus* (Yu and Mott, 1994).

[e] Species include *Bulimus striatulus japonicus* (Yamashita, 1964).

[f] Including *Carassius* sp. (Yu and Mott, 1994).

[g] Species include *Parafossarulus striatulus* (Yu and Mott, 1994).

[h] Species include *P. parva* (Yu and Mott, 1994).

[i] Species include *Bellamya aeruginosa* (Yu and Mott, 1994).

[j] Species include *P. parva* and *Cyprinus carpio* (Yu and Mott, 1994).

2.3.2. *Echinochasmus japonicus* Tanabe, 1926

The genus *Echinochasmus* Dietz, 1909 is characterized by a plump, sometimes elongated, body and the presence of a head collar with a dorsally interrupted crown of spines (Yamaguti, 1958). More than 40 species are known, and four species infect humans; *Echinochasmus japonicus*, *Echinochasmus perfoliatus*, *Echinochasmus liliputanus*, and *Echinochasmus fujianensis* (Yu and Mott, 1994). *Echinochasmus japonicus* was first reported in Japan from experimental animals fed metacercariae from freshwater fish; it is now known to be distributed widely in the Far East (Table 4), particularly in humans in the Republic of Korea (Chai and Lee, 2002) and Anhui, Fujian, Guangdong, Guangxi, and Jiangsu provinces of China (Lin et al., 1985). In six counties of Fujian and Guangdong provinces, China, the infection rate among residents was 4.9% (178/3639); in the same areas, the infection rate was 39.7% in dogs and 9.5% in cats (Yu and Mott, 1994).

2.4. *Nanophyetus salmincola*

Nanophyetus salmincola (Chapin, 1926) Chapin, 1927 (syn. *Troglotrema salmincola* Witenberg, 1932) belongs to the Nanophyetidae Dollfus, 1939, and infects various mammals including humans, the dog, cat, raccoon, and fox, and three species of birds on the Pacific coast of North America and Canada, and Eastern Siberia (Millemann and Knapp, 1970; Beaver et al., 1984). It is minute, pyriform, and possesses two large testes in the posterior half of the body. Its snail host is *Oxytrema silicula* and the second hosts are salmonid (trout, salmon) and non-salmonid fish (Millemann and Knapp, 1970). Nanophyetiasis is endemic in the far-eastern part of Russia including Amur and Ussuri valleys of Khabarovsk territory and north Sakhalin (Yu and Mott, 1994). In local ethnic minorities, the prevalence is 20%, and reaches up to 60% in some localities. In the USA, 20 human cases have been reported since 1974 (Eastburn et al., 1987). Infected people may experience mild diarrhea, abdominal discomfort, and eosinophilia. In animals such as dogs, foxes, and coyotes, however, the fluke has been shown to be the vector of a rickettsia, *Neorickettsia helmintheca*, which causes a serious and often fatal systemic infection known as ‘salmon poisoning’, which has not been reported in humans. Another species, *Nanophyetus schikhobalowi*, described from natives of far-eastern Siberia, is regarded as a subspecies, *N. salmincola schikhobalowi*; the major difference from *N. salmincola* is that this subspecies is apparently not a vector for the rickettsial organism (Millemann and Knapp, 1970).

2.5. Concluding comments

Effective prevention and control of the fish-borne trematode infections discussed above have been and will be difficult to attain in Southeast Asia as long as there is such a strong link of these diseases to poverty. Current strategies such as use of chemotherapy to reduce morbidity, interrupting transmission, and reducing risky human behavior (World Health Organization, 2004) are reasonable and logical. However, because of local constraints, deeply embedded cultural traits, and inadequate national priorities, it is problematic whether this strategy will be implemented sufficiently to have significant public health impact anytime soon. Compounding this difficulty is a number of gaps in knowledge and technology that should be addressed to facilitate implementation of any control efforts:

(i) Improved diagnostic tools are badly needed, especially those that can differentiate the various species;

(ii) Guidelines for designing and implementing epidemiological studies are needed in order to obtain the impact data required by public health agencies in setting priorities;

(iii) The role of reservoir hosts in maintaining transmission in the absence of infected humans needs investigation in order to design sustainable control strategies;

(iv) Social/anthropological studies are needed to better understand the cultural and behavioral traits of people with regard to food choices in order to develop education strategies aimed at influencing risky behavior;

(v) Development of improved aquaculture systems that can prevent or mitigate the transmission of trematodes; and

(vi) Long-term pilot control projects are needed to compare efforts targeted at multiple high risk factors identified in risk assessment studies with the current mass chemotherapy strategy.

3. Diphyllobothriasis

This is the most important fish-borne zoonosis caused by a cestode (tapeworm) parasite. Species of the genus *Diphyllobothrium* (Order Pseudophyllidae, Family Diphyllobothriidae) are responsible for most reported cestode infections in humans. The zoonosis occurs most commonly in countries where it is a frequent practice to consume raw or marinated fish. At least 13 of about 50 species of *Diphyllobothrium* have been reported from humans (Table 5). All are gastrointestinal parasites as adults in a variety of piscivorous birds and mammals. The intermediate hosts include both freshwater and marine fish, especially anadromous species. Although not generally considered a serious zoonosis, there are indications that its frequency and distribution is increasing in some regions, probably because of social and economic change. Even where it may be declining in humans, the cestode is widely distributed in the wild among fish, mammal and bird hosts, a significant zoonotic reservoir (Dick et al., 2001).

3.1. Life cycle and distribution

These tapeworms are among the largest parasites of humans, and may, as adults in the intestine, grow to 2–15 m in length. Characteristic of the order, the scolex has a dorsal–ventral sucking groove (or bothrium) that functions as a holdfast. The strobila may contain up to 3000 proglottids. Life cycles are known for only a few of the species, but those that have been described are complex, requiring three hosts for completion (Rausch and Adams, 2000); additional or paratenic hosts may also be involved. In general, after the egg hatches in water, the motile embryo (coracidium) is ingested by a copepod, and develops to the first larval stage (procercoid). When an infected copepod is ingested by the second intermediate host (freshwater, anadromous or catadromous fish), the larva is released, enters the tissues of the host and develops to the second stage, plerocercoid; the sites of development in the fish may differ according to species of *Diphyllobothrium* (Dick et al., 2001). The plerocercoid stage is infective for the final host, usually fish-eating mammals or birds, and when the fish is

Table 5
Species of *Diphyllobthrium* reported from humans[a]

Species	Piscine hosts[b]	Other definitive hosts[b]	Geographic distribution[c]
Diphyllobothrium alascense	Burbot, Smelt	Dogs	Kuskokwim Delta, Alaska
Diphyllobothrium cameroni	Marine fishes	?[d]	Japan
Diphyllobothrium cordatum	Marine fishes	?	Northern Seas, Greenland, Iceland
Diphyllobothrium dalliae	Freshwater fish (*Dallia pectoralis*)	Gulls, Dogs	Alaska, Siberia
Diphyllobothrium dendriticum	Freshwater fish (Salmonids, Coregonids, Burbot, Grayling)	Fish eating birds and mammals	Circumpolar; introduced elsewhere
Diphyllobothrium hians	Marine fishes	?	North Atlantic; North Sea?
Diphyllobothrium klebanovski	Salmonids	?	Eastern Eurasia, Sea of Japan, Sea of Okhostsk; Alaska?
Diphyllobothrium lanceolatum	*Coregonus*	?	North Pacific, Bearing Sea
Diphyllobothrium latum	Pike, Burbots, Percids	Dogs, Bears	Fennoscandia, western Russia, North and South America; reported from Cuba, Korea
Diphyllobothrium nihonkaiense	Salmon	?	Japan
Diphyllobothrium pacificum	Marine fishes	Sea Lions, Fur Seals	Peru, Chile, Japan
Diphyllobothrium ursi	Red salmon	Bears	Alaska, British Columbia
Diphyllobothrium yonagoensis	Salmon	?	Japan, eastern Siberia

[a] Data summarized from Adams and Rausch (1997); Dick et al. (2001).

[b] Major or reported hosts listed; some species are likely to be found to have wider host ranges after further investigation.

[c] Distributions are listed for human host records.

[d] Likely fish eating birds and/or mammals.

consumed, the parasite develops rapidly in the intestine. The host specificity of these species appears to be quite broad (Table 5). Although *Diphyllobothrium latum* is most often reported from humans, especially in the holoarctic region, *Diphyllobothrium dendriticum* is frequently encountered in circumpolar areas and in areas where it has been accidentally introduced, such as South America (Torres et al., 2004). Other important species are *Diphyllobothrium nihonkaiense* in Japan, *Diphyllobothrium klebanovskii* in eastern Eurasia and *Diphyllobothrium pacificum* along the Pacific Coast of South America.

Because diphyllobothriasis is considered a mild illness and is not normally reportable, our understanding of the global distribution of this parasite infection is somewhat fragmentary and based on limited human and fish surveys or clinical case reports. Sturchler (1988) estimated that there were about 9 million human infections in the 1970 s, but the accuracy of this figure currently is doubtful, and may even be an underestimate. Although *Diphyllobothrium* is generally associated with cold water intermediate and definitive hosts, there are sporadic case reports from warm locales including the Middle East and Malaysia (Abo-Shehada and Ziyadeh, 1991; Rohela et al., 2002), although the sources are not clear; confusion with sparganum infections makes reports from such areas somewhat problematical.

Globally, the incidence of human infections has declined in recent years, particularly in North America (Kingston and Kilbourn, 1989; Dick et al., 2001) and Europe (Dupouy-Camet and Peduzzi, 2004). Until 1982, diphyllobothriasis was a reportable disease in the USA and the Centers for Disease Control (CDC) estimated that about 125–200 cases occurred during the period 1977–1981 (Ruttenber et al., 1984). CDC now estimates there may only be several dozen cases occurring annually in the USA (Deardorff, 1991). Most North American cases occur in the Great Lakes region and Alaska, although there are cases reported elsewhere. During 1981, CDC reported that 52 people residing in the west coast states of the USA became infected with *Diphyllobothrium*, apparently from fresh salmon shipped from Alaska (Ruttenber et al., 1984). Surprisingly, 1% of schoolchildren in Baton Rouge, Louisiana carried *D. latum* according to a survey (Christian and Perret, 1974). The source for these infections appears not to have been investigated.

A recent discovery soon to be reported by C. Estran and colleagues in France revealed that a patient became infected with *D. nihonkaiense* from a salmon (*Oncorhynchus keta*) imported from the Pacific Coast of Canada. This is the first report of this species occurring outside of Asia; this may reflect either a new focus or a previously undetected presence in the Eastern Pacific (Estran, C., Year, H., Delauney, P., Gari-Toussaint, M., Dupouy-Camet, J., Marty, P., unpublished data).

Most reported human infections in South America occur in Chile, Peru and Argentina (Von Bonsdorff, 1977; Dick et al., 2001). The first case in Chile was reported in 1950 (Neghme et al., 1950), and was attributed to infection of rainbow trout, which had been introduced to local lakes, by contamination of the aquatic environment by tourists and immigrants from North America. Currently, the prevalence of diphyllobothriids in some Chilean lake districts ranges from 0.1 to 2.8% (Torres et al., 2004). The presence of the marine species *D. pacificum* in humans in Peru has been estimated to be about 1.6% (Miranda et al., 1967), which is in line with recent findings from the analysis of ancient coprolites of the Chiribaya Culture populations (700–1476 AD) in southern Peru (Holiday et al., 2003), suggesting that this zoonotic species has persisted in the region for a very long time.

A recent analysis of 20 years of diphyllobothriasis case records and surveys in Europe indicates that while this zoonosis has declined overall, especially in the former ‘hot spot’ Scandinavian countries, it persists in several regions (Dupouy-Camet and Peduzzi, 2004). Currently Switzerland, Sweden, Finland and Estonia report more than 10 cases per year (440 in Estonia in 1997), while Lithuania, Poland, Hungary, Italy and France average 2–10 cases annually. Only sporadic cases occur in Norway, Austria, and Spain. Most of the cases in Switzerland, France and Italy occur in the Alpine Lakes region. In Finland, the national prevalence has declined since 1981 when it was 1–4% (Raisanen and Puska, 1984).

Diphyllobothriasis is a common infection in Far-East Russia, where *D. klebanovskii* is considered the important zoonotic species (Muratov and Posokhov, 1988; Lloyd, 1998; Muratov, 1990). The parasite is widespread in all the major river drainages east of the Urals, including those of the Lena, Kolyma and Indigirka rivers (Suvorina and Simonova, 1993). The Amur River region is also an endemic area (Muratov and Posokhov, 1988; Khodakova et al., 1996), as are the coastal area of the Okhotsk Sea where human prevalences range from 1.0 to 3.3% (cited in Lloyd, 1998). A major new focus has apparently developed during the 10 years since the completion of the Krasnoyaek Reservoir on the Enisel River; one survey revealed a prevalence of 7.7% in people living along the reservoir shore (Ko, 1995).

Diphyllobothriasis is frequently reported in Japan, especially along the coast of the Sea of Japan, averaging about 100 cases per year since the 1970 s (Oshima, 1984). Until recently, most infections were considered due to *D. latum*. However, recent taxonomic studies strongly suggest that the majority of infections are due to *D. nihonkaiense* (Yamane et al., 1989; Dick et al., 2001). Infections by other species also cannot be ruled out because other species are known in the region, such as *Diphyllobothrium yonagoensis* (Yamane et al., 1981; Kamo et al., 1988; Dick et al., 2001). As an example, in 1996 a large outbreak in Shizuoka Prefecture was discovered to be caused by another diphyllobothriid, *Diplogonoporus grandis*. Since 1894 there have been more than 100 cases caused by this species in Japan (Kino et al., 2002a, b).

Until recently, diphyllobothriasis has not been considered common in the Republic of Korea. Between 1921 and 2001, only 28 cases were reported and the results of a national prevalence survey for parasites revealed a prevalence of only 0.004% (Lee et al., 2001). However, the growing demand for fresh salmon, and the strong cultural fondness for raw fish may alter the status of this zoonosis in the future (Lee et al., 2001). As with Japan, the systematics of the *Diphyllobothrium* specimens recovered in the Republic of Korea are uncertain because most cases are attributed to *D. latum*, although the fish sources (salmonids) are not typical for this species (Dick et al., 2001, Table 5).

3.2. Epidemiology and factors related to emergence/re-emergence

The source of infection with *Diphyllobothrium* for humans and other definitive hosts is relatively straightforward: consumption of raw or insufficiently cooked or marinated fish. Because of their generally broad host-specificities, *Diphyllobothrium* life cycles are maintained primarily in nature independent of humans, and therefore the cestode is not affected much by elimination from the human population (Adams and Rausch, 1997; Dick et al., 2001; Torres et al., 2004). The host preferences of the various marine or freshwater diphyllobothriid species may be relatively specific for either piscivorous birds or a specific spectrum of mammals such as bears, cetaceans, pinnipeds or humans, and this can be very important in transmission and dissemination.

The zoonosis occurs most frequently in communities that have food preferences for wild-caught fish prepared in a variety of ways. Some notable examples are dishes such as sushi and sashimi, Japanese dishes that have found worldwide popularity, Scandinavian gravlax, strogonina in the Baltics and Eurasia, gefilte fisch, and lightly marinated fish dishes such as ceviche which is growing in popularity in Latin America (Ruttenber et al., 1984; Deardorff and Overstreet, 1990; Deardorff, 1991; Ko, 1995; Adams and Rausch, 1997; Dupouy-Camet and Peduzzi, 2004).

Other risk factors associated with infection are occupation, age and gender (Guttowa, 1970; Adams and Rausch, 1997; Sagua et al., 2000). Although infection rates are usually highest in adults, especially males, there are reports of high rates in children (Christian and Perret, 1974; Khodakova et al., 1996). Occupational risks are exemplified by the often high rates in fishermen who have the habit of eating the roe and livers of their fresh catches, and in women who sample foods under preparation that contain raw fish, especially gefilte fisch.

An increasingly important factor in introducing or sustaining this zoonosis in human communities is the contamination of the local aquatic environment with faeces (Lloyd, 1998; Cross, 2001; Torres et al., 2004; Dupouy-Camet and Peduzzi, 2004). The discharge of improperly treated sewage from lake-side dwellings, hotels and ships is an important source of contamination with eggs. Domestic animals, especially dogs, are another important source of environmental contamination (Adams and Rausch, 1997; Torres et al., 2004), and may help to maintain a natural *D. latum* cycle, which can be amplified by human activities (Dick et al., 2001).

As discussed above (Section 3.1), despite its apparent global decline, diphyllobothriasis appears to have increased in some countries (Oshima, 1984; Deardorff and Overstreet, 1990; Ko, 1995; Torres et al., 2004). The reasons for its persistence or re-emergence are not always clear, and explanations offered are frequently speculative because so little research has been conducted on these issues. Zoonoses such as that caused by *Diphyllobothrium* spp. exist within a continuum that links animal (wild and domestic) and human populations, and this equilibrium may be disturbed by activities such as the intensification of fish production, environmental alterations, translocation of human and animal populations, tourism, changes in fish marketing (export and distribution) systems, and cultural changes in eating habits (Deardorff, 1991; Ko, 1995; Dazak et al., 2000; Murrell, 2002). Certain projections indicate that the future worldwide demand for fish and fish-products will increase substantially (FAO, 1992; World Health Organization, 1995), creating increasing pressure to exploit the marine environment for food (Deardorff, 1991). The growing awareness of the nutritional benefits of fish and fish products, the preferences in many countries for raw or lightly cooked foods, and the rising affluence in both developing and developed countries make this a reasonable prediction. This increased demand may increase the risk of diphyllobothriids entering the human food chain by increasing the harvesting and export of fish from areas of high endemicity. Higher risks for urban populations may also arise because of the incentive for exporters to ship fresh (non-frozen) fish by air to gain a competitive edge in the market (Deardorff and Overstreet, 1990; Kaferstein, 1994; Nawa et al., 2001). The global market in fish exports is quite large. For example, Europe and Canada, both endemic for diphyllobothriids, supply about one-third of the USA demand for seafood (Deardorff, 1991). In the Republic of Korea, the demand for salmonids has increased with rising per capita incomes, and this has stimulated increased production of farmed salmonids. This increase in production concerns public health workers because of its link to the risk of diphyllobothriasis, which has occurred more frequently in the country in recent years (Lee et al., 2001). It should be emphasized here, however, that there is little to implicate farm-raised salmonids in transmission of diphyllobothriids to humans; wild salmonids are at highest risk of becoming infected with diphyllobothriids and represent a major reservoir of infection. Freshwater non-salmonids are also important in certain regions, especially for infection of *D. latum*. Even among salmonid hosts not all species play a similar role. For example, *Oncorhynchus nerka*, which spends extended periods in freshwater lacustrine systems prior to descending to the ocean, may be more important than other species of Pacific salmon in transmitting *Diphyllobothrium ursi* because of its greater vulnerability to human and animal fishing.

Seemingly unrelated environmental changes may also have unexpected effects on the epidemiology of this zoonosis. It has been suggested that the increase in infections by *D. pacificum* during the 1975–2000 period in Northern Chile was related to the cyclic appearance of El Nino phenomena in the Eastern Pacific, which not only affect fish populations but also that of the primary definitive host, the sea lion (Sagua et al., 2000). Another example is the increased risk of diphyllobothriid infection of fish because of growing marine mammal populations in the Northwest Pacific, a result of the 1972 Marine Mammal Protection Act (Deardorff, 1991). Conversely, climatic events have been identified as having a negative effect on fish-borne anisakids (Section 3) in the Western Pacific by causing changes in the abundance of appropriate intermediate and definitive hosts (Ishikura et al., 1998). Effects of climate changes like these reflect the complexity of the aquatic food webs and the unpredictability of responses by biological systems.

The stocking of imported fish in new aquatic habitats may be a significant risk for spreading diphyllobothriids, by providing potential intermediate hosts in the event of egg contamination. The appearance of *D. latum* in Argentina and Chile has been attributed to the introduction of rainbow trout (*Oncorhynchus mykiss*) and brown trout (*Salmo trutta*) in the early 20th century from North America. Later these fish became infected by immigrants and tourists who, through poor sanitary practices, contaminated the aquatic environment with eggs. This led eventually to substantial areas becoming endemic for diphyllobothriasis (Torres et al., 2004). However, the identity of the *Diphyllobothrium* reported from salmonid fish in Chile has been questioned because elsewhere *D. latum* fish intermediate hosts are typically non-salmonids (e.g. pike, perch, see Table 5) (Dick et al., 2001), and it has been suggested that the *Diphyllobothrium* infecting trout and humans in Chile may be another species, endemic to the region, such as *D. dendriticum* (Dick et al., 2001). A similar confusion concerning the role of *D. latum* in Japan existed until recently (see below). Regardless, the risks from introducing new potential fish hosts into locales where zoonotic parasites may already exist are often unappreciated or ignored in human activities driven mostly by socioeconomic motives.

While translocations of humans from endemic areas pose risks for the introduction of diphyllobothriids into new locations, a new 'emergence' of diphyllobothriasis may not be 'new' at all due to confusion about the origins of existing species of the parasite. For example, a long-standing controversy has centered around the idea that *D. latum* was introduced into North America by Scandinavian immigrants, although others have suggested instead that *D. latum* was already present in North America prior to European immigration. Recently, Dick et al. (2001) concluded that based on existing data and the results from their own experimental and field work, the life cycle of *D. latum* became well established in Canadian wilderness lakes without the participation of humans, and that this distribution has changed little during the past 100 years, evidence that favors a pre-European introduction in North America. They suggest, however, that phylogenetic analysis of the genotypes of *D. latum* from Alaska, Siberia and Europe may be the best means for settling the issue.

3.3. Issues and research needs

There is general agreement among experts in this field that the overriding obstacle to clarifying the distribution, host-associations, and epidemiology of diphyllobothriids, especially *D. latum*, is the poor state of the systematics of the genus (Stunkard, 1965; Andersen and Halvorsen, 1978; Matsuura et al., 1992; Adams and Rausch, 1997; Dick et al., 2001; Holiday et al., 2003). The great difficulty in differentiating morphologically the plerocercoids and the adult strobila or proglottids of the various species, has produced confusion among researchers about the specific host ranges of the species, and therefore hindered the understanding of the epidemiology of the zoonoses in North and South America, Far-East Asia and Eurasia (Von Bonsdorff, 1977; Yamane et al., 1989; Muratov, 1990; Revenga, 1993; Zhang, 1996; Dick et al., 2001; Lee et al., 2001; Holiday et al., 2003; Torres et al., 2004). Misunderstandings of the host associations for the freshwater species, *D. latum* and *D. dendriticum* have caused misinterpretations of their epidemiology in specific locales. Research carried out in recent years has convincingly demonstrated that the fish intermediate hosts for *D. latum* are primarily non-salmonid fish such as pike and perches, while *D. dendriticum* utilizes salmonid and coregonid species. The sites of pleurocercoid infection within the fish also differ between the two species (Dick and Poole, 1985; Andersen et al., 1987; Andersen and Gibson, 1989; Dick et al., 2001). The confusion over *D. latum* in Japan was resolved when careful study of the diphyllobothriids from man was identified as a new species, *D. nihonkaiense,* from salmon (*Oncorhynchus gerbuscha* and *Oncorhynchus masu*) and the species *D. yonagoensis* from marine fish (Yamane et al., 1986; Kamo et al., 1988). In Siberia in the 1980 s, it was also discovered that diphyllobothriasis transmitted from salmonid fish (*O. gorbuscha* and *O. keta*) was not, as long believed, *D. latum* but a new species, *D. klebanovskii* (Muratov and Posokhov, 1988). The recent discovery of *D. nihonkaiense* in salmon (*O. keta)* from the Canadian Pacific Coast (Gulf of Alaska) is a good example of why the current taxonomy and mapped distributions of the diphyllobothriids are questionable, since this species may have long been present in this region—just undetected because of confusion with other species of *Diphyllobothrium*.

Although the identification of plerocercoids from fish by morphological criteria is very difficult (Margolis and Arthur, 1979), progress in overcoming this obstacle has been made in recent years, particularly for the freshwater species (Dick and Poole, 1985; Yamane et al., 1986; Andersen et al., 1987; Andersen and Gibson, 1989). However, identifications based on morphological characters for marine species remain troublesome.

Molecular approaches that have proved so powerful in resolving other parasite taxonomic problems have only recently been applied to the diphyllobothriids. Molecular investigations have shown that the morphological variation seen within *D. dendriticum* populations has a genetic basis (De Vos et al., 1990). Ribosomal genes have been identified that can differentiate between the two most important freshwater species, *D. latum* and *D. dendriticum* (De Vos and Dick, 1989). Molecular markers for differentiating *D. latum* and *D. nihonkaiense* have also been reported (Matsuura et al., 1992). Further efforts towards developing molecular tools for diagnostic use and for phylogenetic analysis should be strongly encouraged if many of the issues associated with this zoonosis, such as the origins and distributions of *D. latum* (see Section 3.2) are to be resolved. An important application of such tools should be a strategic validation of genetic markers for definitively identified adult parasites and their larval stages. This can provide the molecular foundation for identifying life history stages for the various species of *Diphyllobothrium*, vital to a full understanding of transmission and distribution.

A second topic that warrants greater attention and evaluation is the potential for enhancing this zoonosis though increased exploitation of fisheries, marine mammal population changes, and major climatic changes. Although largely speculative, the risks discussed in Section 3.2 that could facilitate the transmission of the diphyllobothriids—such as increased consumer raw food preferences and the global marketing of fish—need careful evaluation if public health and natural resource agencies are to make effective policy. Such studies need support and higher priority in research funding than has been the typical in the history of this zoonosis. The argument for greater priority could be strengthened by linking all fish-borne zoonoses (both parasitic and microbial) to their common denominator—the effect of change on the production of fish and fish products—and structuring the research around multidisciplinary and multisectoral collaborations.

4. Anisakiasis

Anisakiasis (anisakidosis) refers to infection of people with larval stages of nematodes belonging to the families Anisakidae or Raphidascarididae. Although cases of human infection have been reported with worms from a number of species within these families (Beaver et al., 1984; Smith and Wootten, 1987; Bouree et al., 1995), the two genera most often associated with anisakiasis are *Anisakis* and *Pseudoterranova*. Anisakiasis occurs when people ingest third stage larvae found in the viscera or muscle of a wide range of fish and cephalopod mollusc species. Humans are accidental hosts in the life cycle, and the parasites almost never develop further within the human gastrointestinal tract. Nevertheless, anisakiasis is a serious zoonotic disease, and there has been a dramatic increase in its reported prevalence throughout the world in the last two decades.

4.1. Life cycle and distribution

The higher-level taxonomy of the superfamily Ascaridoidea is uncertain (Fagerholm, 1991; Anderson, 1992), but recent molecular studies using mitochondrial DNA (mtDNA) and nuclear ribosomal DNA (rDNA) sequences provide provisional support for a monophyletic origin of the family Anisakidae, which includes the genera *Anisakis* and *Pseudoterranova* (Nadler and Hudspeth, 2000). Anisakids typically utilise marine mammals or piscivorous birds as definitive hosts, with aquatic invertebrates and fish as intermediate or paratenic hosts.

Adults of *Anisakis* spp. are found mainly in the gastrointestinal tract of cetaceans (dolphins, porpoises and whales), and adults of *Pseudoterranova* spp. in pinnipeds (seals, sea lions and walrus), although the definitive host range of most species is still incompletely known (Anderson, 1992). Eggs are shed in the faeces, and embryonate and hatch in the ocean, releasing free swimming, apparently third stage larvae (Køie et al., 1995). The larvae are ingested by crustaceans, such as decapods, copepods or amphipods, where they grow within the haemocoel. Fish and cephalopod molluscs become infected by eating crustaceans containing third stage larvae, which penetrate the intestine and invade the tissues of the paratenic host, where they may continue to grow or become encapsulated (Anderson, 1992). Definitive hosts are usually infected by eating fish or cephalopods containing the larvae.

As people usually become infected with anisakids by eating larvae contained within the paratenic host, the distribution of larval nematodes within the tissues of the host is epidemiologically important. This distribution appears to be very variable, and may be affected by the species of parasite (Anderson, 1992), the fish species infected and the environmental conditions to which the fish are subjected after capture (Roepstorff et al., 1993). Some studies have found that larval nematodes migrate from the visceral organs to the muscle after the death of the paratenic host, and that this migration may be enhanced by the cold storage or processing of ungutted fish (Van Thiel et al., 1960; Smith and Wootten, 1975; Hauck, 1977; Abollo et al., 2001). Other studies, however, have not been able to demonstrate post-mortem migration of larvae in the paratenic host (Cattan and Carvajal, 1984; Roepstorff et al., 1993). Another important aspect of the life cycle of species of both *Anisakis* and *Pseudoterranova*, from an epidemiological perspective, is that larval parasites will readily transfer from one paratenic host to another and piscivorous fish can therefore accumulate very large numbers of larvae (Smith and Wootten, 1987; Anderson, 1992).

Species identification in the Anisakidae has traditionally been complicated by a lack of distinguishing morphological characteristics, particularly in larval worms. Historically, therefore, only two major zoonotic species were recognised: the ‘herring worm’ *Anisakis simplex* and the ‘codworm’ *Pseudoterranova* (syns *Phocanema*, *Terranova*) *decipiens*, both with a potentially cosmopolitan distribution (Smith and Wootten, 1987; Oshima, 1987). Recent molecular genetic studies, however, have shown that both of these morphospecies actually comprise a number of sibling species, genetically differentiated and often with distinct geographical and/or host ranges. At least three species have been described within the *A. simplex* complex: *A. simplex* (*sensu stricto*), found in the northern Atlantic, *A. simplex* C, found in the northern Pacific and southern waters below 30°N; and *Anisakis pegreffi*, found in the Mediterranean Sea (Mattiucci et al., 1997). Paggi et al. (1991) also described three species within the *Pseudoterranova* complex: *P. decipiens* A in the north east Atlantic and Norwegian Sea, *P. decipiens* C in the north west Atlantic and Barents Sea, and *P. decipiens* B throughout northern waters; where the ranges of these species overlapped, they appeared to preferentially utilise different definitive host species. Further genetic studies are required to confirm the geographical and host ranges of these species, and to establish their relationships with other species of *Anisakis* and *Pseudoterranova*, which have been described on morphological criteria.

A very large number of fish species act as paratenic hosts for species of *Anisakis* and *Pseudoterranova*. Differences in host range between species have been found. For example, *A. simplex* and *Pseudoterranova* spp. occur most often in benthic or demersal fish, while *A. pegreffi* is found more frequently in pelagic fish (Paggi et al., 1991; Anderson, 1992; Mattiucci et al., 1997; Abollo et al., 2001). These differences appear to be related more to geographic distribution and feeding habits of hosts than to behavioural or physiological host preferences of the parasites.

4.2. Pathology and epidemiology

Live anisakid larvae may be ingested when people eat raw, insufficiently cooked, smoked or marinated paratenic hosts. The larvae are killed by heating to temperatures greater than 60 °C for at least a minute or freezing at −20 °C for at least 24 h (Acha and Szyfres, 1987; Smith and Wootten, 1987).

Clinically, human anisakiasis can take a number of forms, depending on the location and histopathological lesions caused by the larvae. Larvae may remain in the gastrointestinal tract, without penetrating the tissues, causing an asymptomatic infection, which may only be discovered when the worms are expelled by coughing, vomiting or defecating (Acha and Szyfres, 1987). In invasive anisakiasis, larvae penetrate the gastric or intestinal mucosa, or more rarely other sites such as the throat (Beaver et al., 1984; Acha and Szyfres, 1987; Amin et al., 2000). There is some evidence that gastric invasion is more often associated with infections by *Pseudoterranova* spp. and intestinal invasion with infections by *Anisakis* spp. (Oshima, 1987). Symptoms of gastric anisakiasis usually appear 1–7 h after consumption of fish, while intestinal anisakiasis usually manifests 5–7 days after fish consumption. In both cases, there is severe pain, with nausea and vomiting (Acha and Szyfres, 1987; Oshima, 1987). Histopathological examination of invasive anisakiasis usually reveals the worm embedded in a dense eosinophilic granuloma in the mucosa, often with localized or diffuse tumours in the stomach or intestinal wall (Beaver et al., 1984; Acha and Szyfres, 1987).

Endoscopic examination can often be used to provide a definitive diagnosis for gastric anisakiasis, but clinical diagnosis of intestinal anisakiasis is difficult and requires careful examination of clinical symptoms and patient history. From clinical symptoms, gastric anisakiasis is often misdiagnosed as a peptic ulcer, and intestinal anisakiasis as appendicitis or peritonitis (Acha and Szyfres, 1987; Oshima, 1987). Although immunological diagnosis of anisakid infection shows potential, it is complicated by antigenic cross-reactivity with other ascarids (Iglesias et al., 1996).

In recent years, it has become clear that anisakiasis is often associated with a strong allergic response, with clinical symptoms ranging from isolated swellings to urticaria and life threatening anaphylactic shock (Alonso et al., 1997; Audicana et al., 2002). Most cases of allergy reported to date have originated in Spain, and have involved an elevated immunoglobulin response to *A. simplex*; the strength of allergic reactions to other anisakid species is not yet known. The *A. simplex* allergens which invoke a hypersensitivity reaction appear to be highly resistant to heat and freezing (Audicana et al., 2002), raising the prospect of an allergic response to parasitised fish products which have been prepared in a way which would normally kill nematode larvae. At this stage, it is not known whether initial sensitisation can also occur to allergens from dead parasites, or whether a priming infection with live parasites is required to induce sensitisation (Audicana et al., 2002).

Anisakiasis occurs through the world, with foci in north Asia and western Europe. Of the total (about 20,000) cases of anisakiasis reported to date, over 90% are from Japan (where approximately 2000 cases are diagnosed annually), with most of the rest from the Netherlands, Germany, France and Spain (Feldmeier et al., 1993; Bouree et al., 1995; Audicana et al., 2002). As diagnostic methods improve, however, more cases are being reported from other areas of the world, including the USA (Amin et al., 2000), Canada (Couture et al., 2003), Chile (Mercado et al., 2001), New Zealand (Paltridge et al., 1984) and Egypt (Cocheton et al., 1991).

As with diphyllobothriasis, the prevalence of anisakiasis is clearly related to traditions of consuming raw, lightly cooked or marinated fish, such as Japanese sushi and sashimi, Dutch salted or smoked herring, Scandinavian gravlax, Hawaiian lomi-lomi and Latin American ceviche. The risk of anisakid larvae in these dishes may be enhanced if the fish are eaten whole (because worms are often found in the viscera rather than the flesh of fish) or if the fish have been kept whole for some time after capture, rather than gutted immediately (because worms may migrate from the viscera to the flesh after death of the fish). Most control measures for anisakiasis emphasise the importance of immediate evisceration of captured fish, and cooking or freezing fish product prior to consumption (Acha and Szyfres, 1987; Abollo et al., 2001). Consumption of live larvae in raw or undercooked fish, however, is not necessarily the only way in which the parasite can cause disease; in some cases there is evidence that occupational exposure to fish products may be sufficient to trigger an allergic response to anisakid allergens (Purello-D'Ambrosio et al., 2000).

In the last 30 years, there has been a marked increase in the prevalence of anisakiasis throughout the world. This is probably due to a number of factors. First, the increase in reported cases coincides with new diagnostic techniques, particularly endoscopy; prior to the development of the gastrofiberscope many cases of gastric anisakiasis were probably misdiagnosed (Oshima, 1987). Second, as with diphyllobothriasis and other fish-borne parasitic diseases, the increasing global demand for seafood and a growing preference for raw or lightly cooked food, especially in many western countries, increases the risk of parasite exposure (McCarthy and Moore, 2000). Third, there has been speculation that greater regulatory controls over the exploitation of marine mammals has led to increasing population sizes of potential definitive hosts (Oshima, 1987; Bouree et al., 1995; McCarthy and Moore, 2000), although it should be recognised that the relationship between definitive host population size and parasite population size is not straightforward for parasites such as anisakid nematodes, which have a complex, multi-host life cycle.

4.3. Issues and research needs

There are a number of areas in which further research is necessary to understand the life cycle and transmission dynamics of anisakid nematodes and the epidemiology of anisakiasis. Of primary importance is a thorough systematic study of *Anisakis*, *Pseudoterranova* and related genera using molecular genetic techniques. Allozyme electrophoresis and sequencing of rDNA and mtDNA have already produced unexpected findings at a variety of taxonomic levels. These studies have identified non-monophyletic groupings within the superfamily Ascaridoidea (Nadler and Hudspeth, 2000) and found previously described morphospecies in European and North American waters to consist of several genetically differentiated biological species (Paggi et al., 1991; Mattiucci et al., 1997). This work needs to be extended to other areas of the world, such as Mexico (Castillo-Sanchez et al., 1998), Argentina (Cremonte and Sardella, 1997), the Philippines (Petersen et al., 1993), Australia (Doupé et al., 2003), New Zealand (Wharton et al., 1999) and Kuwait (Sey and Petter, 1998) where anisakids of uncertain taxonomic designation have been found in fish hosts. Molecular genetic analyses will also provide an essential tool for basic ecological studies of anisakids. Even for well-described species, such as *A. simplex* and *P. decipiens*, we still do not know the full extent of their geographical distribution, host range and prevalence rates in definitive, intermediate or paratenic hosts.

Another issue which remains unresolved is the extent of post mortem migration of anisakid larvae from viscera to muscles in their fish hosts. This is important from an epidemiological viewpoint because many control measures for anisakiasis emphasise the importance of immediate evisceration of captured fish to prevent post-mortem migration of larvae (Acha and Szyfres, 1987). If in fact post mortem migration does not occur, then this practice should not be encouraged, because the disposal of infected viscera at sea may result in infections of fish, which feed on discarded viscera (Abollo et al., 2001).

One of the most important findings about anisakiasis to emerge in recent years has been the discovery of hypersensitivity reactions to anisakid allergens (Audicana et al., 2002). This has not only led to the recognition of a different suite of pathological reactions to anisakid infections, which may be manifested in people handling, as well as ingesting fish products, but also the thermostability of the allergens involved means that standard precautions of freezing or cooking fish may not provide protection against an allergic response. An important issue, which remains unresolved, is whether a priming infection with a living parasite is needed to induce sensitization.

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