

An Overview of Fish-borne Nematodiasis among Returned Travelers for Recent 25 Years– Unexpected Diseases Sometimes Far Away from the Origin

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Abstract: Along with globalization of traveling and trading, fish-borne nematodiasis seems to be increasing in number. However, apart from occasional and sporadic case reports or mini-reviews of particular diseases in particular countries, an overview of fish-borne nematodiasis among travelers have never been performed. In this review, we gathered fish-borne nematodiasis among travelers for recent 25 years by an extensive global literature survey using appropriate keywords, e.g. travelers diseases, human infection, anisakiasis, gnathostomiasis, capillariasis, sushi, sashimi, ceviche, *Gnathostoma*, *Pseudoterranova*, *Anisakis*, *Capillaria*, etc., as well as various combinations of these key words. The Internet search engines PubMed, Medline, Google and Google Scholar were used as much as possible, and the references of every paper were checked in order to identify useful and reliable publications. The results showed unexpectedly high incidence of gnathostomiasis and low incidence of anisakidosis. The different incidence values of the infection with several fish-borne zoonotic nematode species are discussed, as well as some epidemiological aspects of the infections. The difficulties of differential diagnosis in non-endemic countries are emphasized. It is concluded that travelers must avoid risky behaviors which can lead to infection and that physicians and health authorities must advise travelers on the risks of eating behaviors during travel.

Key words: Fish-borne nematode, zoonosis, human infection, public health, traveler

INTRODUCTION

Traveling abroad is nowadays very frequent and the number of people involved increased drastically in the last years. According to the World Tourism Organization destinations around the world welcomed 956 million international tourists from January to September 2016 [1]. Most of these people probably expose themselves to a wide range of pathogens, including helminth parasites, or adopt some risky behaviors favoring the infection with a wide variety of pathogens. In spite of extensive reviews and alerts about the risk factors for travelers involved in

these problems [2-4], the number of cases of imported infectious diseases has been rather increasing with time.

Travelers are accidentally infected with fish-borne parasites. The contact with new ethnic dishes, the novelty of a different way of “cooking” in the so-called exotic countries, are factors leading people to try different kind of foods which may cause infection with various nematode species. The symptoms of the infection can appear almost immediately or later, sometimes after having returned home. Therefore, the incidence and geographic range of certain fish-borne parasitic diseases may increase and constitute emerging zoonotic helminth infections that have newly appeared in a population or have existed but are rapidly increasing in incidence or geographic range [2].

A number of studies have been made about zoonotic fish-borne nematodiasis among returned travelers. Most of them are simple case reports [5-10]. Several researchers produced re-

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views on a particular parasite like *Gnathostoma* spp. [11-20], or *Capillaria philippinensis* [21,22] where the infection of travelers is referred to in a particular country or region. As far as the authors are aware there are only 3 studies reporting all the cases of ocular gnathostomiasis all over the world between 1937 and 2005 [23], and till 2010 [18] and further updated until 2017 [24]. Clément-Rigolet et al. [15] presented a list of imported gnathostomiasis to western countries (immigrants and travelers) since 1980 by chronological order of the reports, listing 42 cases.

However, a world survey of fish-borne nematodiasis among returned travelers has never been conducted. In this review, the authors report the world known cases of human fish-borne nematodiasis among returned travelers, in a tabulated form, indicating for each parasite species, the country of infection, the country of the returned traveler, the number of cases and the references. A general discussion is provided on the different aspects of this interesting problem.

FISH-BORNE PARASITIC ZOOSES

Fish-borne parasitic zoonoses is a major and important part of food-borne parasitic zoonoses. More than 10 years ago, Chai et al. [25] wrote an excellent review on this topic, and the review was further expanded as a monograph entitled "Food-Borne Parasitic Zoonoses: Fish and Plant-Borne Parasites" by Murrell et al. [26]. Among fish-borne parasitic zoonoses, much attentions and efforts have been directed towards fish-borne trematodiasis, especially of small fluke infections [27-29], but not directed against nematodiasis. Humans may be infected with fish-borne nematodes if the fish are eaten alive, raw or undercooked. For some nematode species, the parasites may be ingested when people eat raw meat of mammals, birds, amphibians and reptiles, which may be involved as intermediate or paratenic hosts in the life cycle of the fish-borne nematodes. The fish-borne nematodes most frequently found in humans are the members of Anisakidae, i.e., *Anisakis* spp. [30] and *Pseudoterranova* spp. [31], followed by the Gnathostomatidae *Gnathostoma* spp. [12], and *Capillaria philippinensis* [21]. Some other species such as *Hysterothylacium aduncum* [32,33], *Contracaecum* spp. [34], *Eustrongylides* spp. [35], *Diocotophyme renale* [36] are also known as fish-borne zoonotic pathogens in humans, but their infections are very rarely reported than those of the afore-mentioned species. Although *A. cantonensis* infection in humans can occur by consuming land-

snails and rarely shrimps [37], a case was reported to have occurred after eating uncooked fish [38].

In some Asian countries there is a strong tradition of eating raw or undercooked fish prepared in several ways. In addition to globally known "Sushi" and "Sashimi" in Japan [12], similar food habits like "Koi pla", "Pla ra", "Pla som" and "Som fak" in Thailand [39] are present in Laos and Cambodia. In the Philippines, "Kinilaw", "Sabaw" and "Sukba" are known as the traditional food habits, which enable fish-borne zoonotic parasite infections. Moreover, there are a number of other different ways of preparing raw fish in other countries like "Ceviche" in Peru, "Gravlax" in Nordic countries, "Boquerones in vinegar" in Spain, or "Crudo" in Italy. These dishes, especially Japanese "Sushi", are very popular in their original country, and actually a number of them and imitated ones have been spreading all over the world where they constitute a kind of "fashionable" healthy food and now has become a strong risk of acquiring fish-borne nematodiasis [12]. In addition to the cultural changes of eating habits, increase of global trading and traveling, expansion of fishing areas and development of cold transportation systems caused considerable changes in epidemiology of fish-borne parasitic zoonoses [40-44].

Anisakidosis

Anisakidosis is the most representative fish-borne nematodiasis with approximately 20,000 reported worldwide of which >90% were from Japan and most other cases from coastal Europe (Netherlands, Germany, France and Spain), USA (west coast and Hawaii in particular) [45]. Most cases of human infections are caused by *Anisakis simplex*, *A. physeteris* and *Pseudoterranova decipiens* (previously known as *Phocanema decipiens*) and far less frequently by other members of the family Anisakidae such as *Anisakis pegreffii*, *Contracaecum* species, *Hysterothylacium* species, *Raphidascaris* species and *Thynnascaris* species [45,46]. *Anisakis pegreffii* is a sibling species of *A. simplex*. Recently, the etiologic agents of human anisakiasis in Korea, which were morphologically *Anisakis* type I larvae, were molecularly confirmed to be *A. pegreffii* larvae [47,48]. Moreover, most of the *Anisakis* type I larvae detected in 7 fish species from the Yellow Sea and the South Sea in Korea were also identified as *A. pegreffii* [49].

The term anisakidosis refers to disease caused by any member of the family Anisakidae, whereas anisakiasis is caused by members of the genus *Anisakis* and pseudoterranovosis by the genus *Pseudoterranova* [46].

In relation to the traditional custom of eating "Sushi" and

“Sashimi”, anisakidosis is still a public health issue in Japan [50,51]. Along with the global popularization of “Sushi” and “Sashimi”, cases have been reported from unexpected countries like Australia [34], Austria [52], Brazil [53], Germany [54] etc. In particular, anisakidosis is an emerging public health of Korea [55,56]. Anisakidosis due to *Pseudoterranova* sp. infection is emerging in Chile [57-59] and Peru [60,61].

Apart from direct mechanical and chemical damages of gastrointestinal mucosa by anisakid larvae, recently antigenic components of anisakid larvae are proven to cause food allergy and gastrointestinal allergy [45,46,62,63]. Thus, pathogenesis of anisakid parasites may be much more complicated than we thought.

Intestinal capillariasis

Intestinal capillariasis is a disease caused by an auto-infection of the intestinal nematode, *Capillaria philippinensis*. Human infection occurs by ingesting freshwater or brackish water fish harboring the infective stage larva of this parasite. The endemic of this disease was first found in northern Luzon of the Philippines [21] and then central to northeast Thailand [64]. In Egypt, the first case was found in Cairo [65] and the parasite is now established and spread to the Upper Egypt [66]. In Taiwan, the first case was reported by Hwang et al. [67], and since then, a total of 30 cases have been recorded, mostly among 2 Taiwanese aboriginal tribes, suggesting that *C. philippinensis* has established in Taiwan [68]. Among those 30 cases, 5 cases have a history of traveling either to the Philippines (2 cases) and/or Thailand (4 cases). In addition to those endemic countries, sporadic cases have been reported from several Asian countries; the first case in China was recently recorded in the Hainan Island [69]. Three sporadic cases without international travel history have been reported in India [70]. In Japan, 6 cases including 1 Japanese traveler returned from Malaysia and Singapore [71] and 1 Thai immigrant worker [72], have been reported. In Korea, 7 cases have been reported including 3 indigenous [73-75] and 4 cases of possible overseas infection. Among 4 cases of overseas infection, 2 cases were in Saipan (one Korean resident in Saipan [76] and one Korean traveler to Saipan [77]) and 1 case each of a temporary resident in Indonesia [74] and the Philippines [78]. Three cases were reported also from Lao PDR [79], 2 of which were the seasonal migrant workers returned from the endemic area of Thailand. One case each was reported from various countries; from Iran [80]; from Italy infected in Indonesia [5]; 1 case of Egyptian

woman in Dubai, UAE [81]; one case of Colombian cocaine dealer arrived at Madrid, Spain [82].

Gnathostomiasis

Gnathostomiasis is one of the typical fish-borne nematodiasis caused by eating raw or undercooked fish meat containing infective third stage larvae. The disease has long been known to be endemic in Northeast to Southeast Asia, especially Thailand and Japan [83]. Since 1970, outbreaks of this disease have been reported from Latin America, mostly from Mexico and Ecuador [84,85]. *Gnathostoma* spp. are apparently the most common fish-borne nematodes found among travelers. *Gnathostoma spinigerum* is endemic in the Southeast and East Asia whereas *G. binucleatum* is endemic in some Latin American countries (Mexico, Ecuador and Peru), and in some countries the disease is considered a public health problem [84], namely in Mexico where over 10,000 cases of the illness were reported by 2010 [85]. Humans can be infected by ingesting raw or poorly cooked fish, snakes, frogs, and some mammals which have the advanced third stage larvae and constitute second intermediate or paratenic host. Some people are infected by ingesting live fish – some Japanese people enjoy swallowing live loaches in drinking whisky or Japanese rice wine. Several human infections due to this behavior were described [86]. Apparently *Gnathostoma* spp. may be found in any fish species, and the worms have been collected from a number of different freshwater and brackish water fish specimens. Another way of contamination is drinking water containing crustaceans (*Cyclops*) which serve as intermediate hosts [87,88]. The infection can also be contracted by the penetration of skin of food handlers by the nematodes larvae in infected meat or use of contaminated meat as poultice [89].

Eustrongylides and *Dioctophyma renale*

Eustrongylides is, together with other 2 genera, *Hystrix* and *Dioctophyma*, constituting of the fish-borne nematode Family Dioctophymatidae. While *Hystrix* and *Eustrongylides* are naturally intestinal parasites of fish-eating birds, *Dioctophyma* is a parasite of mammals infecting in the kidney [90]. Until recent discovery of a female *Eustrongylides* worm from the lower limb skin in Sudan [35], all 5 cases of *Eustrongylides* infection in humans were reported from USA with the recovery of a larval stage worm from the peritoneal cavity [91-95]. *Dioctophyma renale* infection in humans is also extremely rare. When Beaver and Theis (1979) discovered the first human case of subcuta-

neous nodular lesion by a *D. renale* larva [96], they have made an extensive literature review on all previously reported *D. renale* infection in humans and listed 13 cases, all of which were the kidney/urinary tract involvement with mature adult worms [96]. Since then, several sporadic case reports have been appeared in the literature until the most recent case from Iran [97]. Although several case report papers referred that over 20 cases of *D. renale* infection in humans have been reported [98,99], the exact number of cases have not been determined. Now we are conducting an extensive literature survey on *Diocetophyma renale* infection in humans and found a total of more than 40 cases [Nawa et al. manuscript in preparation].

DATA COLLECTION AND THE CRITERIA OF TRAVELER

To collect the fish-borne nematodiasis cases reported in the literature, an extensive internet electronic search was conducted using appropriate key-words, like nematode human infections, emerging diseases, neglected diseases, anisakiasis, gnathostomiasis, capillariasis, sushi, sashimi, ceviche, traveler diseases, *Gnathostoma*, *Pseudoterranova*, *Anisakis*, *Capillaria*, etc., as well as various combinations of these key-words. The internet search engines, PubMed, Medline, Google and Google Scholar were used, and the references of every paper were verified in order to identify useful and reliable publications. We recognized it is practically impossible to track all the available literature, but it is hoped that nearly all the cases reported were tracked.

For the purposes of this study we consider a returned traveler as a traveler who had been abroad for a period no longer than 6 months before returning to the original country. Therefore, people who lived several years abroad and returned infected to the original country [74,76-78,99-101] were not considered as travelers. People who immigrated to other countries and developed there the disease [13,102-110] were not considered as travelers either. Moore et al. [111] referred 12 persons infected with *Gnathostoma*, who were examined in the Hospital for Tropical Diseases, in London. The patients were original, or visited a number of countries (China, South Korea, Bangladesh, India, Thailand, SE Asia, Vietnam, Thailand, etc.) where gnathostomiasis is frequent, and some reported to have eaten raw fish. Some of the patients were immigrants, but the number of travelers or immigrants in their study is not clear, and the duration of the visits in the case of travelers was not

indicated-only one case which no doubt could be considered a traveler was included in the present paper. In the study of illness among travelers returned to France from the tropics, Ansart et al. [112,113] referred the occurrence of several cases of gnathostomiasis. However, the countries visited were not detailed, neither the kind of traveler (tourist or immigrant, etc.). For these reasons those cases are not included in the present study. Similarly, a case of intestinal capillariasis detected in a Colombian man in Spain described by Drona et al. [82] was not considered because of the unclearness of the travel history of the patient. In the literature survey we found 3 cases of travelers infected with fish-borne nematodes but, acquired the disease by ingesting other hosts than fish (frogs, boar, duck, chicken and pork) [9,114-117]. These cases were included in the Table 1. Considering the several *Gnathostoma* species can cause human infection, we indicated the species names only when the surgically removed specimens were identified by morphological and/or molecular examination, because immune-serological methods alone do not always provide definite evidence of species identification due to strong cross-reaction of antibody beyond the species [118-120]. Therefore, even when the causative species were identified by serological tools, we referred to as *Gnathostoma* sp. within the Table 1 and the corresponding presumptive species is indicated in brackets.

FISH-BORNE NEMATODIASES AMONG TRAVELERS

The number of infection cases of returned travelers, parasite species, country of origin, country where the infection was presumably acquired, and references are indicated in Table 1.

According to the data collected, 100 cases of fish-borne nematode infections have been reported in returned travelers in 22 countries, namely, Argentina, Austria, Australia, Belgium, Brazil, Canada, England, France, Germany, Israel, Italy, Japan, Korea, Laos, Peru, South Africa, Spain, Switzerland, Thailand, Taiwan, the Netherlands, USA and Venezuela. The causative nematode species were *Angiostrongylus cantonensis* (1 case), *Anisakis simplex* (6 cases in total), *Capillaria philippinensis* (8), *Gnathostoma malaysiae* (2), *G. spinigerum* (3), *G. binucleatum?* (7), *G. doloresi?* (1), *G. spinigerum?* (27) and *Gnathostoma* sp. (46).

DISCUSSION

In this review, surprisingly gnathostomiasis is the most fre-

Table 1. Cases of infection with fish-borne nematodes among returned travelers

Parasite	From	To	No. of cases	Reference
<i>Angiostrongylus cantonensis</i>	Tahiti	France	1	[15,38]
"Anisakiasis"	Not indicated	Australia	2	[34,121]
"Anisakiasis"	Chile	Belgium	1	[122]
"Anisakiasis"	Belgium	Israel	1	[123]
<i>Anisakis simplex</i>	USA	Austria	2	[124]
<i>Capillaria philippinensis</i>	Indonesia	Italy	1	[5]
<i>C. philippinensis</i>	Saipan island	Korea	1	[77]
<i>C. philippinensis</i>	Philippines & Thai	Taiwan	1	[68]
<i>C. philippinensis</i>	Philippines	Taiwan	1	[68]
<i>C. philippinensis</i>	Thailand	Taiwan	3	[125]
<i>C. philippinensis</i>	Malaysia/Singapore	Japan	1	[71]
<i>Gnathostoma malaysiae</i>	Myanmar	Japan	1-2	[126]
<i>G. spinigerum</i>	Vietnam	Japan	1	[115]
<i>G. spinigerum</i>	Philippines	USA	1	[127]
<i>G. spinigerum</i>	Thailand	USA	1	[128]
<i>Gnathostoma</i> sp. (<i>G. binucleatum</i> ?)	Brazil or Colombia?	Belgium	1	[129]
<i>Gnathostoma</i> sp. (<i>G. binucleatum</i> ?)	Peru	Brazil	1	[130]
<i>Gnathostoma</i> sp. (<i>G. binucleatum</i> ?)	USA	Colombia	1	[131]
<i>Gnathostoma</i> sp. (<i>G. binucleatum</i> ?)	Mexico	USA	1	[132]
<i>Gnathostoma</i> sp. (<i>G. binucleatum</i> ?)	Mexico	France	1	[7]
<i>Gnathostoma</i> sp. (<i>G. binucleatum</i> ?)	Mexico	Spain	1	[133]
<i>Gnathostoma</i> sp. (<i>G. binucleatum</i> ?)	Peru	Switzerland	1	[6]
<i>Gnathostoma</i> sp. (<i>G. doloresi</i> ?)	Sri Lanka	Korea	1	[134]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	China	Australia	15	[135] ^a
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Thailand	Canada	1	[14]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Hungary	France	1	[136]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Southeast Asia	Germany	1	[137]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Thailand	Germany	1	[138]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Laos	Germany	1	[8]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Peru	Germany	1	[139]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Thailand or Indonesia	Spain	1	[140]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Thailand	Spain	1	[133]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Vietnam	Switzerland	1	[141]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Southeast Asia	The Netherlands	2	[142]
<i>Gnathostoma</i> sp. (<i>G. spinigerum</i> ?)	Thailand or Indonesia	Switzerland	1	[143]
<i>Gnathostoma</i> sp. ^b	Colombia	Argentina	1	[10]
<i>Gnathostoma</i> sp.	Vietnam	Korea	1	[9]
<i>Gnathostoma</i> sp.	Botswana	England	2	[144]
<i>Gnathostoma</i> sp.	Thailand or Myanmar	Austria	1	[117]
<i>Gnathostoma</i> sp.	Borneo	England	1	[111]
<i>Gnathostoma</i> sp. ^c	Cambodia	France	3	[145]
<i>Gnathostoma</i> sp. ^c	Thailand	France	1	[145]
<i>Gnathostoma</i> sp. ^c	Vietnam	France	1	[145]
<i>Gnathostoma</i> sp.	Brazil	France	1	[146]
<i>Gnathostoma</i> sp.	Cambodia	France	2	[147]
<i>Gnathostoma</i> sp.	Laos	France	2	[147]
<i>Gnathostoma</i> sp.	China	France	2	[147]
<i>Gnathostoma</i> sp.	Myanmar	France	1	[147]
<i>Gnathostoma</i> sp.	Japan	France	2	[147,148]
<i>Gnathostoma</i> sp.	Sri Lanka	France	1	[147]
<i>Gnathostoma</i> sp.	Thailand	France	1	[147]
<i>Gnathostoma</i> sp.	Vietnam	France	2	[147,149]
<i>Gnathostoma</i> sp.	Mexico	France	2	[147]
<i>Gnathostoma</i> sp.	Bali	France	1	[148]
<i>Gnathostoma</i> sp.	Brazil	Japan	1	[16] ^d
<i>Gnathostoma</i> sp.	South Africa	Japan	1	[16] ^d
<i>Gnathostoma</i> sp.	Cambodia	Japan	1	[16] ^d
<i>Gnathostoma</i> sp.	USA	Venezuela	1	[24]
<i>Gnathostoma</i> sp.	Ecuador	Peru	1	[150]
<i>Gnathostoma</i> sp.	"Caribbean"	Peru	1	[150]
<i>Gnathostoma</i> sp.	China	Spain	2	[111]
<i>Gnathostoma</i> sp.	Zambia	South Africa	1	[151]
<i>Gnathostoma</i> sp.	Botswana	South Africa	1	[152]
<i>Gnathostoma</i> sp.	Tanzania	USA	3	[153]
<i>Gnathostoma</i> sp.	Vietnam	USA	1	[114]
<i>Gnathostoma</i> sp.	Zambia	USA	1	[151]
<i>Gnathostoma</i> sp.	Turkey or Thailand	USA	1	[13]
<i>Gnathostoma</i> sp.	Thailand	USA	1	[154]

^aA personal communication from A. Fuller in Reference [135].^bThis case was reported without immunodiagnosis and the validity of the description was questioned by Joob and Wiwanitkit [155], and the same case was commented by Rodríguez-Morales et al. [156]. See replies by Orduña et al. [157,158].^cMénard et al. [145] reported *Gnathostoma hispidum* from one of the patients identified by histological observation. However, the country where the traveler came from was not indicated.^dUnpublished data from Y. Nawa in Reference [16].

quent fish-borne nematodiasis among global travelers, whereas the number of anisakidosis cases was extremely low in spite of its high incidence in some countries like Japan. One simple and most possible explanation for this difference is due to the difference of incubation period of the diseases. Generally, a few days to few months are required for the development of clinical manifestations of gnathostomiasis after the infective larvae in uncooked fish were ingested [84,85]. Thus, travelers with peculiar signs and symptoms of gnathostomiasis will visit clinicians after they have returned their home country where clinicians are not familiar with such a strange disease. In contrast, the vast majority of anisakidosis patients develop their signs and symptoms of acute abdomen within few hours after ingestion of the larvae in “Sushi”, “Sashimi” etc. during their travel and are treated immediately by endoscopic specialists. In endemic countries like Japan, anisakiasis cases of travelers from overseas might thus not appear as case reports because the disease is so common.

As an alternative explanation of extremely low incidence of anisakidosis among international travelers, the responsible species and the sources of fish used for “Sushi” and “Sashimi” in restaurants should be considered. According to Nawa et al. [12], fish which are preferentially served in qualified Japanese restaurants are less contaminated or even free of *Anisakis*. However, some less expensive marine fish like mackerel and mollusks like squid, which are also often used for “Sushi” and “Sashimi” in cheap local restaurants, are many times heavily infected with *Anisakis* and the risk of infection is higher. Salmon is the fish species most commonly used for “Sushi” and “Sashimi” worldwide, and the large part of salmon are originated in aquaculture net cages facilities where they are intensively fed with processed feeds. A number of studies showed that such fish are free from *Anisakis simplex*, although some specimens may be infected through the consumption of contaminated small invertebrates and fish, which can enter the net cages. It was demonstrated that the proportion of infected fish in the farmed species is extremely low [159-161], and this fact may probably contribute decisively for the surprisingly low prevalence of anisakidosis in returned travelers. However, low anisakiasis infection in farmed fish does not necessarily mean low prevalence infection rates in humans eating this kind of food-an evaluation of the amount of food ingested would be necessary to integrate all the facts involved in the human infection by *Anisakis* spp.

Another explanation for low incidence of anisakidosis or

any other fish-borne nematodiasis is the underestimation due to inaccurate diagnosis. It may be questioned the validity of the number of fish-borne nematodiasis cases described so far in returned travelers. In some countries like Australia, where the popularity of consuming raw or undercooked fish is great, there is only one case report of human infection [34]. Shamsi [121] explained that probably anisakidosis is underestimated in the country due to the sometimes difficulty to diagnose of infection, and suspected the presence of more hidden cases in the country. Verhame and Ramboer [122] considered also that the disease is underestimated in Belgium and in most other European countries. According to these authors, “It seems likely that only the tip of the iceberg is seen and that many of the less severe cases remain under-diagnosed, the condition being considered transient gastroenteritis”. As reported by Sakanari and McKerrow [162], the disease is often misdiagnosed and, in a clinicopathological study of 92 cases of anisakiasis in Japan, “over 60% of cases were diagnosed preoperatively as appendicitis, acute abdomen, gastric tumour or cancer, ileitis, cholecystitis, diverticulitis, tuberculous peritonitis, and cancer of the pancreas”. Therefore, the number of cases of anisakiasis in returned traveler may be in fact much higher than the few cases reported so far.

As can be seen in Table 1, the number of gnathostomiasis cases among travelers is unexpectedly high compared with other fish-borne nematodiasis. This unexpected result is, as has been discussed above, at least in part attributed to the nature of pathogenesis of *Gnathostoma* larvae. Different from anisakid larvae in the stomach to cause extra-rapid clinical manifestation, usually several days to months are required for *Gnathostoma* larvae after being ingested to cause clinical symptoms in humans. Thus, the disease mostly developed after returning from the travel and it is difficult for patients to link the disease with their experience of having ethnic dishes. Together with rapid movement of the skin lesions, unknown causes of the disease often terrify the patients.

While reviewing gnathostomiasis cases among travelers, we recognized that some *Gnathostoma* species identifications may not be accurate because, in many of the cases, they were diagnosed based on clinical features and the results of serodiagnosis, but not based upon the morphological and/or molecular observation of the worms. Even when worms were obtained from patients, it is extremely difficult to distinguish *G. spinigerum* and *G. binucleatum* from each other. In fact, many misdiagnosis of *G. binucleatum* as *G. spinigerum* have been reported

until recent development of molecular identification [84,85]. Because those 2 species distribute geographically different places, travel history of the patients is helpful to speculate the causative species [84,85]. Since the chance of detection of worms in surgical specimen is extremely low and the immunodiagnostic tools are not sensitive enough for identification of causative pathogen at the species level, development of more specific (and of course sensitive) diagnostic methods is awaited.

Intestinal capillariasis caused by a nematode, *Capillaria philippinensis*, is rather a rare but famous fish-borne nematodiasis because of its high mortality. Due to auto-infection, delayed diagnosis/treatment often resulted in death due to protein-losing gastroenteropathy. After the discovery of its first outbreak in the northern Luzon of the Philippines in the 1960s [21,22], its endemic areas have expanded to Thailand [64], Egypt [66] and Taiwan [67,68]. Various species of freshwater or brackish water fish play a role of the intermediate hosts, the source of human infection, and human infection occurs after ingesting raw or undercooked fish. As shown in Table 1, capillariasis is rather a rare disease among travelers – just 8 cases, and all of them have a history of consuming raw fish. One of the reasons for this low incidence might be because the endemic areas are generally remote from the common tourism areas. However, it should be noted that the establishment of *C. philippinensis* in the new endemic locality has been caused by migration of infected people from an endemic area. Such an example was seen in Pudoc West and several other regions in the Philippines [21]. Lu et al. [68] suggested the possibility of some of the about 200,000 foreign laborers in Taiwan who originated from major epidemic areas might contribute to the spread of the disease in Taiwan. Although the emergence of intestinal capillariasis in Egypt is often considered to be due to large number of migrant labors from the endemic areas, the exact reasons still remain obscure [163]. These observations suggest that the disease transmission by immigrants is much more important than by travellers for the epidemiology of *C. philippinensis* infection in humans.

Although *Angiostrongylus cantonensis* is principally not a fish-borne nematode parasite, its intermediate snail hosts are the main source of causing human infections and are often sold in fish markets. Humans may contract the infection by ingesting infected snails or paratenic hosts like prawns, crabs and frogs, and may be also by consuming vegetables contaminated with larvae from the degenerated/crashed body of intermedi-

ate or paratenic hosts. In this literature survey, we found 2 references [38,164] mentioning about travelers of possible infection with *A. cantonensis*. In 1 case (Southeast Pacific to USA) [164], the patient was serologically diagnosed as eosinophilic meningitis due to *A. cantonensis* infection. Although the patient ate seafoods, he has no clear history of ingesting snail intermediate hosts or other possible source of infection [164]. In another case (Tahiti to France), the patient has a history of eating raw fish, which is considered as the source of infection [38], so that this case is included in our list (Table 1). However, in the latter case, possible infection by eating shrimp, vegetables or any other kind of contaminated food materials cannot be ruled out. High prevalence of *A. cantonensis* larvae in shrimp in Tahiti has been reported [165]. In terms of importation of *A. cantonensis* from non-endemic to endemic areas, a possible role of rodents traveling on cargo ships is evident by molecular identification of the geographical isolates of *A. cantonensis* [166].

Finally, in this review, we were unable to find any report of traveler's infections with *Hysterothylacium* spp., *Contraecaecum* spp., *Eustrongylides* spp., or *Dioctophyme renale* although these are known as zoonotic fish-borne nematodes with records of human cases [32-36]. This is not surprising because human infections with these nematode species in general are extremely rare and only few cases have been recorded sporadically worldwide. The infection chance of travelers with these species is supposed to be highly limited.

In conclusion, this is the first extensive literature review on fish-borne nematodiasis among travelers. The results showed unexpectedly high incidence of gnathostomiasis and low incidence of anisakidosis. This discrepancy seems to be due primarily to the difference of the incubation period of the diseases. Other possibilities are also discussed.

Many countries where the fish-borne nematodiasis exists, a variety of popular dishes containing raw fish, as well as the high number of fish species infected were used in the confederation of ethnic dishes of raw fish. This may be one of the reasons for the relatively large variety of cases in returned travelers (infected in 30 countries for travelers belonging to 22 countries). In terms of clinical manifestation, most of fish-borne nematodiasis listed in this review have unique signs and symptoms. Even so, most of atypical forms are probably under-diagnosed [111,149].

In general, only few clinicians and laboratory workers in non-endemic areas are familiar with these diseases [11,74] and

most clinicians have difficulties in recognizing the symptoms of the infections [110,167]. Early diagnosis of the infection is important because in cases of *Capillaria philippinensis* infection, delay in diagnosis can cause severe life threatening disease with high mortality rates [125]. According to Lu et al. [68], delayed diagnosis of capillariasis for more than a year was reported from Japan, Korea, Egypt and India.

In summary, we can conclude that

1. The consumption of raw, alive, or undercooked fish, both marine and freshwater, may originate travelers infection caused by zoonotic fish-borne nematodes belonging to different species.
2. Returned travelers may constitute a mean of spreading the parasites in countries where the parasites did not exist.
3. Physicians and health authorities must advice travelers on the dangers of risk behaviors in order to not acquire the infection.

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CONFLICT OF INTEREST

The authors declare they have not conflict of interest.

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