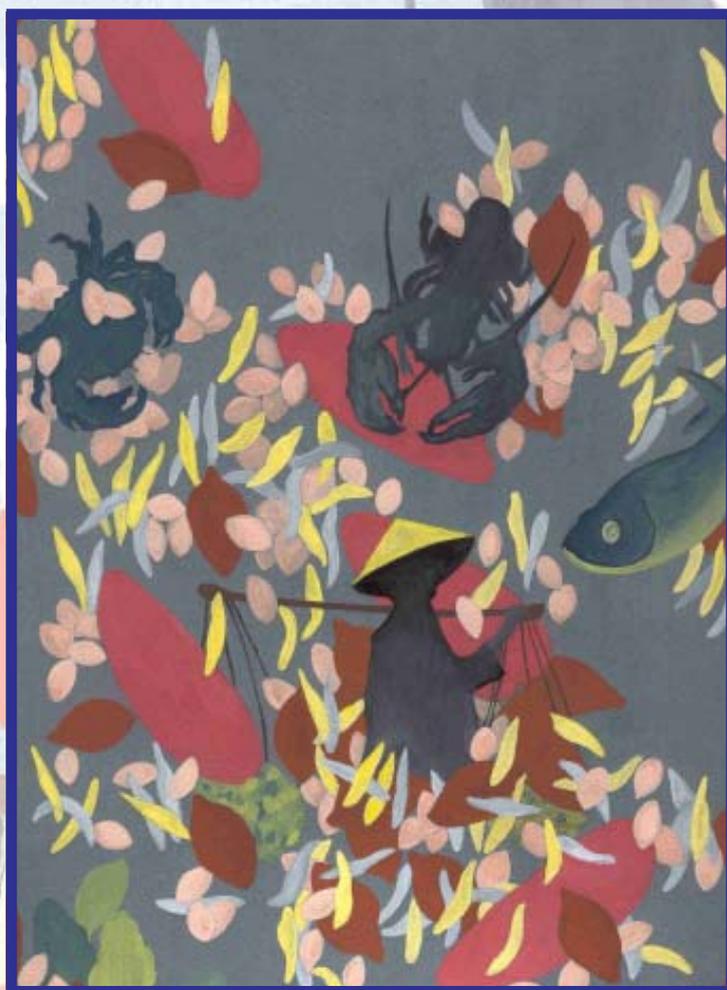


REPORT

JOINT WHO/FAO WORKSHOP ON
**FOOD-BORNE TREMATODE
INFECTIONS IN ASIA**



Ha Noi, Viet Nam
26-28 November 2002



World Health Organization
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Convened by:

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NOTE

The views expressed in this report are those of the participants in the Joint WHO/FAO Workshop on Foodborne Trematode Infections in Asia and do not necessarily reflect the policies of the Organization.

This report has been prepared by the World Health Organization Regional Office for the Western Pacific for governments of Member States in the Region and for those who participated in the Joint WHO/FAO Workshop on Foodborne Trematode Infections in Asia, which was held in Ha Noi, Viet Nam from 26 to 28 November 2002.

SUMMARY

The World Health Organization (WHO) and Food and Agriculture Organization (FAO) held a joint workshop in Ha Noi, Viet Nam from 26 to 28 November 2002 to review the knowledge on foodborne trematode (FBT) infections, to discuss the possible measures for prevention and control of these infections and to inform Member States of the urgency for the implementation of control activities.

FBT infections affect the health of more than 40 million people throughout the world and are particularly prevalent in WHO's South-East Asia and Western Pacific Regions. These parasites originate an unacceptable burden of suffering and mortality and cause serious damage to aquaculture, which is a valuable source of food and employment in developing countries.

FBTs present particular epidemiological and clinical features that should be carefully considered for the development of appropriate preventive and control measures. Transmission to humans is almost entirely caused by consumption of food containing infective metacercariae. The distribution of these infections is highly focal, depending on the food habits of people and on the presence of susceptible snails. FBTs also present low host specificity, and a high number of definitive reservoir hosts can contribute to the contamination of water and snails, making it extremely difficult to control this aspect of the parasite cycle. From a clinical point of view, trematode eggs frequently cannot be detected in the stools or sputum of suspected cases and the disease presents a specific symptomatology, leading to frequent misdiagnoses. Tools such as serology and ultrasonography, which allow a precise diagnosis, are frequently not available in areas where FBT are endemic.

For all these reasons, the public health approach to control FBT should be based on "large-scale chemotherapy". Progress gained with pharmacological intervention should be sustained by practices that prevent the establishment of infection in fish and introduce high standards of food quality control in the commercial aquaculture sector. Health education significantly reduces risk habits and with good sanitation and hygiene represents a foundation for the prevention of parasitic disease.

Countries where FBT infections occur should establish an intersectoral working group to implement public health interventions, ensuring access to treatment for people living where these infections are endemic, and legislate for best practice for eliminating the risk of FBT infection from aquaculture products.

Two drugs are available for "large-scale chemotherapy". Praziquantel, a compound that is exceptionally well tolerated, is the drug of choice for the treatment of infection with most species of FBTs. In the case of fascioliasis, the only FBT infection for which the efficacy of praziquantel is not considered satisfactory, WHO recommends triclabendazole, a drug that has been used for treating fascioliasis for more than 20 years in the field of veterinary medicine; it is now available for human use.

Proper selection of the aquaculture site, the use of high quality water and the training of workers to increase their knowledge and understanding regarding the routes of transmission of the parasites can reduce considerably the contamination of fish with parasites. However, these sanitary practices are not easy to implement in small-scale subsistence fish-farming situations.

Pharmaceutical companies, international organizations and research institutions should collaborate in developing guidelines for surveys (enabling to identify areas and population at risk) and in developing methods for the detection, monitoring and prevention of the emergence of drug resistance in FBTs.

I. INTRODUCTION

A joint WHO/Food and Agriculture Organization (FAO) Workshop on Foodborne Trematode Infections in Asia was held in Ha Noi, Viet Nam from 26 to 28 November 2002. What follows is a summary of the proceedings from this workshop.

1.1 Objectives

Foodborne trematode (FBT) infections in Asia affect human health in countries where the helminths are endemic, threaten to restrict economic opportunities arising from aquaculture and are of major concern for food safety. These themes were explored in some detail during a WHO Study Group meeting in Manila, October 1993. The Group's report, WHO Technical Report Series No 849 (1), provided the foundation for the Workshop's assessment of the current status of FBT infections in Asia. In addition, over 10 years of experience in dealing with FBTs has elapsed since the Manila meeting; this body of knowledge proved helpful in the formulation of recommendations aimed at reducing the burden of disease due to FBTs and the problem they cause to the aquaculture industry.

The workshop had five major objectives:

- review knowledge of FBT infections in relation to control strategies;
- assess the current public health significance of FBT infections in Asia;
- propose practical measures for controlling morbidity due to FBT infections;
- propose practical measures for reducing and preventing transmission of FBT infections; and
- propose practical measures for the prevention and control of FBT infections in the aquaculture industry.

A glossary of the key terms and abbreviations used in the report is provided in Annex 1.

1.2 Background

1.2.1 Foodborne trematode infections

When a living worm at the metacercarial stage is eaten by a suitable host, human infection with FBT occurs. Depending on the species of FBT, infective metacercariae are found encysted on or in fish, crabs, crayfish and plants living in freshwater. Consumption of raw or undercooked freshwater fish, crabs, crayfish and plants carries the risk of infection and disease to people in Asia who live where FBTs are endemic. Countries importing freshwater aquaculture products from Asia must be assured that the best practice for quality control is in operation so that their citizens are protected from FBT infections.

Commonly encountered FBTs in Asia

Trematodes are flukes belonging to the phylum Platyhelminthes which also includes tapeworms. About 70 species of FBTs are known to infect humans. FBT infections are classified as zoonotic infections because they are viewed as animal diseases transmitted to humans. Some infections appear to be rare while others are common and cause serious disease. The species which received most attention at the Ha Noi Workshop are listed in Table 1. Table 2 looks at the number of cases of intestinal trematodes in the Republic of Korea as an example of the extent of the public health concern. Generalizations about the public health significance of a particular species should be considered with caution. Each country must make its own judgements based on the best available local and national information.

Table 1. FBTs of medical importance and public health significance in Asia¹

	Family	Genus	Species	Source of human infection ²	Location in human body
LiF	Fasciolidae	<i>Fasciola</i>	<i>F. gigantica</i>	Plants	Liver and biliary system
			<i>F. hepatica</i>	Plants	Liver and biliary system
			<i>Fasciolopsis</i>	<i>Fas. buski</i>	Plants
LiF	Opisthorchidae	<i>Clonorchis</i>	<i>C. sinensis</i>	Fish	Liver, biliary system and pancreatic duct
			<i>Opisthorchis</i>	<i>O. viverrini</i>	Fish
LuF	Troglotrematidae	<i>Paragonimus</i> ³	Species complex	Crabs and crayfish	Pleural cavity and lungs; occasional brain invasion
IF ⁴	Heterophyidae	<i>Haplorchis</i>	<i>H. taichui</i>	Fish	Mucosa of small intestine
			<i>Metagonimus</i>	<i>M. yokogawai</i>	Fish

LiF – liver flukes; Lu.F – lung flukes; IF – intestinal flukes

¹ The table covers species discussed at the FBT Workshop, Ha Noi, Viet Nam, November 2002. For details of the extent and variety of FBT known to infect humans, see references 1, 2, 3, 4, and 5.

² Infection depends on swallowing metacercariae encysted on or in freshwater organisms which are regularly eaten raw or undercooked. Metacercariae of *Fasciola* have been found floating freely in freshwater.

³ Recent application of DNA technology means that a comprehensive taxonomic revision of this genus is required. Until this work has been completed, use of specific names may lead to confusion.

⁴ See also Table 2.

Table 2. Proven and estimated numbers of human cases infected with intestinal trematodes in the Republic of Korea¹

Species	No of proven human cases in the whole country ²	Estimated no of human infections
<i>Metagonimus yokogawai</i>	> thousands	120 000
<i>Metagonimus takahashii</i>	> 15	20 000
<i>Metagonimus miyatai</i>	> 200	100 000
<i>Heterophyses nocens</i>	> 200	50 000
<i>Heterophyopsis continua</i>	8	10 000
<i>Pygidiopsis stanma</i>	31	50 000
<i>Stellantchasmus falcatus</i>	4	5 000
<i>Centrocestus armatus</i>	1	1 000
<i>Stictodora fascata</i>	1	2 000
<i>Stictodora lari</i>	6	1 000
<i>Echinostoma hortense</i>	> 100	50 000
<i>Echinostoma cinetorchis</i>	4	1 000
<i>Echinochasmus japonicus</i>	4	5 000
<i>Acanthoparpyhium tyosenense</i>	10	1 000
<i>Neodiplostomum seoulense</i>	28	1 000
<i>Plagiorchis muris</i>	1	500
<i>Gymnophalloides seoi</i>	> 100	40 000

¹ Taken from reference 4 and reproduced with permission from Elsevier Limited.

² The population of the Republic of Korea is approximately 47 732 000 (August 2001).

Life cycle of FBTs

FBTs belong to the sub-class Digenea. Digenean trematodes undergo sexual reproduction in their definitive hosts (e.g. humans) and asexual reproduction in their intermediate hosts (snails). In the case of FBTs, eggs pass out of the definitive hosts in the faeces and those which reach freshwater or brackish water, hatch and infect susceptible snails. Development in the snail results in the release of numerous cercariae which swim about until they contact a suitable plant or animal where encystment occurs to form metacercariae (see Table 1). The life cycle is completed and continues when viable metacercariae are swallowed by susceptible definitive hosts.

Host specificity

The FBTs listed in Table 1, and many other less common species, generally show low host specificity. Typically, more than one snail species can serve as the intermediate host where asexual reproduction occurs, many species of water plant can harbour metacercariae of fasciolid species while various species of freshwater crustacean and numerous species of freshwater fish can carry and transport metacercariae. In addition to humans, domesticated animals (dogs, cats, pigs, cattle, sheep, goats, buffaloes), feral animals, rodents, foxes and birds serve as suitable definitive hosts for FBTs. This situation raises several important points for consideration when the control of FBTs is under consideration, including:

- Measures should be taken to reduce the flow of egg-bearing faeces into the freshwater environment of susceptible snails.
- With the current state of knowledge, measures to control FBT infections in definitive reservoir hosts other than humans would appear to be unrealistic and impractical.
- Attempts to eliminate or reduce snail populations, for example by means of molluscides, are likely to have unacceptable environmental consequences.

Comprehensive information about the host ranges of FBTs is to be found in 'Control of Foodborne Trematode Infections' (1).

Metacercariae and transmission

The transmission of FBTs to humans in Asia is almost entirely due to the regular consumption of food containing infective metacercariae. Metacercariae are minute. Even those encysted on the surface of a food item cannot be seen without magnifying aids while those within tissues can easily be overlooked despite careful dissection.

It is important to educate people about the risks to their health from eating raw, pickled or undercooked foods if they live in or visit areas where FBT infections are endemic. Similarly, restaurants, catering agencies and food processing establishments require advice about actions to reduce the risks of transmission including the importance of good hygiene practices and the need to prepare food so that metacercariae are inactivated.

1.2.2 Public health significance of FBT infections in Asia

Epidemiology

Accurate information about the distribution and abundance of FBTs in Asia is essential (a) for assessing the scale of any problems in terms of public health priorities, and (b) for planning, implementing, monitoring and sustaining prevention and control activities.

The WHO Study Group meeting in Manila in October 1993 undertook a thorough review of the known worldwide distribution of FBTs, including estimates of the numbers of people at risk and the number infected with each infection in each country [see Annex 1 and Annex 2 of the earlier report on FBT infections - WHO Technical Report Series No. 849 (1)]. Additional information presented at the FBT Workshop, Ha Noi, November 2002, is provided in Annex 2 of this report.

The distribution of FBTs remains uneven, reflecting the varied food habits and social practices of different groups of people and the ecological interactions between hosts other than humans in the life cycles of FBTs. FBT infections tend to be highly focal because of their dependence on the distribution of species of susceptible snail. These interactions are important because wild fish and crustaceans are a valuable source of protein for many people.

Morbidity

As with all worm-induced disease, morbidity is closely linked to the intensity of the infection or worm burden. The greater the number of worms in a person, the greater the likelihood of symptomatic disease. Many infected individuals will harbour a few worms while a few will have much higher numbers. This overdispersion in the frequency distribution of numbers of worms per host occurs with FBT infections in humans. There is insufficient information about the relation between FBT intensity and morbidity in humans. Nevertheless, it is apparent that serious health problems develop in infected people.

Clinical manifestations of disease (see Table 1)

The pathogenesis of FBTs and pathology of their infections has been reviewed in some detail by Rim (6), IARC (7) and Haswell-Elkins *et al.* (8). A summary follows:

- *Fascioliasis* (from infection with *Fasciola gigantica* and *F. hepatica*)
Abdominal pain, frequently localized to right hypochondrium; anorexia and weight loss; malaise; mild intermittent fever; mild hepatomegaly; jaundice; biliary abnormalities; traumatic and necrotic lesions in hepatic tissue; fibrosis of biliary ducts. Ultrasonography is now readily available for monitoring fascioliasis (WHO Technical Report Series No 723 (9, 10)). Diagnosis of infection usually depends on the detection of *Fasciola* eggs in stool samples.
- *Fasciolopsiasis* (from infection with *Fasciolopsis buski*)
Epigastric pain; may simulate peptic ulcer; facial oedema; urticarial lesions on the body; nausea and vomiting; diarrhoea. Diagnosis of infection usually depends on the detection of *Fasciolopsis* eggs in stool samples.
- *Clonorchiasis* (from infection with *Clonorchis sinensis*)
Anorexia; indigestion; abdominal pain; weakness and weight loss; diarrhoea; jaundice; portal hypertension; ascites; gastrointestinal bleeding; formation of gallstones; inflammation and hyperplasia of the biliary epithelium leading to deposition of fibrous

tissue. Invasion of the pancreatic duct occurs in patients with heavy infections. Cholangiocarcinoma. Severe infection associated with cholangitis, cholecystitis and cholelithiasis. Specific diagnosis based on detection of eggs in stool samples is difficult particularly in light infections and may result in a lower detection rate because: (a) few eggs will be present in light or moderate infections; (b) the eggs are small; and (c) the eggs are similar to those of other species of intestinal trematode.

- *Opisthorchiasis* (from infection with *Opisthorchis viverrini*)
Many of the signs and symptoms are similar to those described for clonorchiasis. With chronic heavy infections, patients present with enlarged gall-bladder, cholecystitis cholangitis, liver abscess and gall stones. Cholangiocarcinoma. Specific diagnosis based on detection of eggs in stool samples is difficult owing to similarity to eggs of other trematode species (including intestinal trematodes).
- *Paragonimiasis* (from infection with *Paragonimus* spp.)
During their association with the human host, lung flukes penetrate the diaphragm, spend time in the pleural cavity and then invade the lung parenchyma. Chest pain; cough with rust-coloured sputum; fatigue; fever; focal haemorrhagic pneumonia; migrating subcutaneous nodes granuloma formation and fibrotic encapsulation in the lung parenchyma. Abdominal pain, decreased appetite and diarrhoea. Flukes migrate to ectopic sites, cerebral paragonimiasis is invariably fatal. Diagnosis of infection usually depends on the detection of eggs in sputum and/or stool samples.
- *Haplorchiasis* (from infection with *Haplorchis* spp.) and *Metagonimiasis* (from infection with *Metagonimus yokogawa*)
Abdominal pain; diarrhoea; lethargy. Symptoms linked to villous atrophy and crypt hyperplasia in response to contact between the flukes and the mucosa of the small intestine. Diagnosis of infection usually depends on the detection of eggs in stool samples.

Carcinoma and FBT infections

Cholangiocarcinoma or cholangiocellular carcinoma (CC) is a malignant tumour arising from the epithelium of the bile duct. In many parts of the world it is the second commonest primary liver cancer (7, 11). CC accounts for about 15% of liver cancers but its occurrence varies from region to region.

Both *O. viverrini* and *C. sinensis* are associated with cholangiocarcinoma (1). There is strong epidemiological evidence to support this claim; the incidence of cholangiocarcinoma in people infected with one or other of these species of fluke is greater than can be explained by chance. Most detailed research has been carried out in Thailand and there can be no doubt that *O. viverrini* is involved with the aetiology of cholangiocarcinoma in that country (12) and this conclusion may be extended to include other countries where *O. viverrini* is endemic (7, 11, 13). Following a case-control study of 103 patients with cholangiocarcinoma, Parkin *et al.*, (14) concluded that two-thirds of cases of the tumour in Thailand could be attributed to infection with *O. viverrini*.

The mechanism by which cholangiocarcinoma arises during infection with *O. viverrini* has been investigated under controlled laboratory conditions using hamsters as experimental hosts. Studies have concentrated on the role of *O. viverrini* infection alone or *O. viverrini* in combination with dimethylnitrosamine (DMN) and other substances. DMN is produced by bacteria in salted fish while some Chinese food products contain nitrates, nitrites and N-nitropyrolidine. The published results of much research in this field have been reviewed in

detail (11, 13). There is compelling evidence of a synergism between *O. viverrini* infection and mutagenic nitrogenous compounds. Suspected mechanisms leading to carcinogenesis include chronic irritation of the bile duct epithelium, nitric oxide formation, intrinsic nitrosation and activation of drug-metabolizing enzymes. Accordingly, the International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence in humans for the carcinogenicity of infection with *O. viverrini* (7, 13).

While it follows that measures aimed at the prevention and control of opisthorchiasis will lead to a reduction in the incidence of cholangiocarcinoma, the significance of the consumption of fish products containing DMN and other compounds should not be overlooked.

Epidemiological evidence indicates that *C. sinensis* is a probable cause of cholangiocarcinoma (13). There is support for that conclusion because cases of cancer in the liver in association with *C. sinensis* infection have been reported from China, Hong Kong (China), Japan and Korea where *C. sinensis* occurs. In 1996 it was reported from Guangzhou, China, that among 10 480 cases of clonorchiasis, 37 also presented with primary liver cancer while among 87 639 patients without clonorchiasis, 44 presented with liver cancer. In the presence of *C. sinensis* there was approximately 1 cancer case per 283 patients and 1 case per 1992 patients in the fluke's absence. With respect to controlled experiments, under certain conditions cholangiocarcinoma can be induced in hamsters infected with *C. sinensis* and exposed to N-2-fluorenylacetamide (FAA) or DMN. In hamsters infected experimentally with up to forty metacercariae of *C. sinensis* while being exposed to FAA, the incidence of CC was found to be significantly greater ($P < 0.05$) in infected animals that survived beyond 25 weeks (11/14) than in uninfected animals (6/17) (15). Six out of eight hamsters developed CC 10 weeks after infection with *C. sinensis* during which time DMN (15 ppm) was added to the drinking water. None of the hamsters in the three control groups (uninfected, uninfected + DMN, infected) developed CC (16, 17, 18).

Mortality

There appears to be little reliable information on mortality rates directly attributable to FBT infections. Death due to fluke-induced cholangiocarcinoma is to be expected (Section 3.2.2) but quantitative information is not readily available (see 1).

Problems of misdiagnosis and diagnosis

Misdiagnosis frequently occurs when patients present with FBT infections. Misdiagnosis leads to additional stress and ill health for patients and is a serious waste of health service resources.

Misdiagnosis of pulmonary tuberculosis

Paragonimiasis may conceal the presence of tuberculosis and is regularly responsible for misdiagnosis of this killer disease. According to WHO, this problem has persisted for more than 100 years (1). Haemoptysis (rust-coloured sputum) is a characteristic sign of paragonimiasis and the cardinal sign of tuberculosis. Radiological findings of paragonimiasis are often indistinguishable from those of pulmonary tuberculosis and, on occasion, lung cancer. The presence of adult *Paragonimus* spp can be confirmed with certainty when the worm's eggs are found in sputum samples. However, egg production and transport from the lungs to the mouth is often erratic so that eggs may not be present if only one sputum sample is collected and examined or if a light infection is present.

Misdiagnosis related to infection with Clonorchis sinensis

Research results from China reveal that the presence of *C. sinensis* and *O. viverrini* led to the following examples of misdiagnosis: chronic hepatitis; acute hepatitis with jaundice; hepatocirrhosis; cholecystitis; cholelithiasis; chronic enteritis; digestive malfunctioning; and ascariasis.

1.2.3 Aquaculture in Asia

The form of aquaculture of most relevance to the workshop concerns that based on freshwater. The persistence and spread of FBT infections depends on habitats of the species of susceptible snail which require freshwater or, in some cases, mildly brackish water for their development. Exposure of susceptible snails to trematode eggs when fresh faeces from infected humans and animals are introduced into water almost guarantees the continuation of the infections. When freshwater fish, food plants, snails and crustaceans occupy or are farmed in the same contaminated water, human health is put at risk.

Aquaculture, whether it occurs in backyard ponds, family farms or industrial systems, has become an important source of much needed food security. Overall, finfish forms 16% of the animal protein in the world's food consumption and 24% of the animal protein in the diet of Asian people. FAO estimates that during 1999 the global production of aquatic products (animal and plants combined) amounted to 42.77 million metric tons (mmt) valued at US\$ 47.87 billion. Over 90% of the world's aquaculture production during 1999 was based in Asia (38.89 mmt) with China contributing 30.04 mmt of aquaculture products to the total. FAO also calculates that some 45% of the global aquaculture is centred on freshwater yielding about 19.4 mmt of finfish; again almost all this fish originates in Asia where FBT infections are endemic.

In addition to the nutritional importance of aquaculture, the activity offers a valuable source of employment, poverty alleviation, cash income, foreign exchange and low-risk entry points for rural development. There is now an overwhelming need for extending the introduction and implementation of measures to control and eliminate FBT infections without impeding the development of freshwater aquaculture. Such measures will improve the health of people in localities where the infections are endemic and will contribute to optimizing the potential for aquaculture to contribute positively to the export earnings of developing countries in Asia.

Aspects of freshwater aquaculture and FBT infections at the subsistence level

Many rural households in Asia include a pond where fish are maintained as a source of food. Human and animal faeces are invariably added to the ponds for nutrient enrichment or carried into them through natural surface drainage after rain. The widespread use of latrines constructed on stilts directly over fishponds or beside them is an important source of contamination. If the faeces contain FBT eggs and if susceptible snails and fish are present in the ponds, the risk of human infection will remain, especially if people persist with their traditional habits of eating raw, pickled or undercooked freshwater fish. In addition, the customers of restaurants will also be at risk of FBT infection if traditional uncooked fish dishes are served based on locally produced fish.

Intermediate hosts of FBT infections

Comprehensive lists of known first and second intermediate hosts of FBTs and the countries where they are found have been published by WHO in Technical Report Series Number 849 (1). Although the significance of each species in the flukes' life cycles is not given or may not be known, controlling FBT infections by targeting intermediate hosts will likely be

difficult. An example of the complexity of such an operation concerns *Paragonimus* spp. The freshwater crabs and crayfish which harbour the metacercariae of *Paragonimus* spp. are not normally cultured but are caught wild, often by children, who eat them partly cooked. More than 80 crustacean species have been reported to be second intermediate hosts of *Paragonimus* spp. in China.

The host lists published by WHO in Technical Report Series No 849 (1) also include the plant species known to support metacercariae of *Fasciola* spp. and *Fasciolopsis buski*.

Aspects of freshwater aquaculture and FBT infections at the commercial level

The present state of freshwater aquaculture in Asia is complex and difficult to separate from full-scale commercial or industrial aquaculture. For example, a fishpond may provide for the family that owns it while surplus is sold locally. According to FAO, the true extent of regional and international trade in aquaculture products is difficult to analyse. Trade in many aquaculture products is not yet well documented in the main producing countries and international trade statistics do not distinguish between wild and farmed origin. Thus, the exact breakdown in terms of farmed and wild origin in international trade is open to interpretation.

Regarding freshwater aquaculture exports from Asia, tilapia exports are reasonably well documented through import statistics from the major importing countries, the United States and Japan.

Aquaculture on a large scale involves the commercial production and distribution of fish fry. Some years ago, Bisseru (20) drew attention to the importation in West Malaysia of metacercariae of *C. sinensis* in fry of *Aristichthys nobilis*. This component of the FBT problem must not be overlooked in programmes to prevent and control infections.

2. PROCEEDINGS

2.1 Justification for FBT Control

2.1.1 Public health priority

There is abundant evidence to show that FBT infections cause serious morbidity in many people in the countries of Asia (Annex 2; Tables 1 and 2). Until more comprehensive epidemiological information is obtained, the extent of the problem will not be fully understood. Two additional features of FBT infections should not be overlooked. First, the distress to patients and the costs to health services of misdiagnosis (Section 3.4) and secondly, the relationship between FBT infections and carcinomas (Section 3.2.2).

Apparently there has been an increase in the consumption of raw or undercooked fish and crabs in some parts of Asia, facilitated partly by population migrations and partly by the commercial provision of these products. There is a need for public health authorities to be vigilant concerning the emergence or re-emergence of FBT infections.

In setting priorities for action in the public health sector, the availability, costs, effectiveness and sustainability of control measures must be assessed. Strategies which offer the greatest good to most people at least cost are important considerations when decisions are held on the public health impact of FBT infections.

2.1.2 Aquaculture priority

There has been a growing awareness in WHO and FAO of the importance of an integrated, multidisciplinary approach to food safety and quality, considering the entire food chain. For aquaculture, the food chain approach recognizes that the responsibility for the supply of fish that is safe, healthy and nutritious is shared along the entire food chain – by all involved with the production, processing, trade and consumption of fish. Stakeholders include farmers, processors, transport operators, distributors, consumers, as well as governments obliged to protect public health. The implementation of the food chain approach requires an enabling policy and regulatory environment at national and international levels with clearly defined rules and standards, establishment of appropriate food control systems and programmes at national and local levels and provision of appropriate training and capacity building.

Development and implementation of Good Aquaculture Practices (GAP), Good Hygienic Practices (GHP) and Hazard Analysis Critical Control Point (HACCP) are required in the food chain step(s). Government institutions should develop an enabling policy and a regulatory environment, organize the control services, train personnel, upgrade the control facilities and laboratories and develop national surveillance programs for FBTs. The support institutions (academia, trade chain) should conduct research on quality, safety and risk assessments and provide technical support to stakeholders. Finally, consumers and consumer advocacy groups should have a major role in educating and informing the consumer about the major safety and quality issues.

2.2 Approaches to the prevention and control of FBT infections

In the public health sector, the aims of FBT control should be: (a) to use chemotherapy in order to reduce the associated morbidity to a threshold below which it is no longer a matter of public health concern; (b) to sustain progress gained in morbidity control and implement measures designed to disrupt transmission leading to the elimination and eventual eradication of infection; and (c) to reduce risk habits such as eating raw or undercooked fish, crustaceans and plants.

In the commercial aquaculture sector, the aims of FBT control should be: (a) to establish practices which prevent the establishment of infection where freshwater fish are farmed; and (b) to introduce high standards of food quality control so that products leaving fish and food processing plants are certified as being safe for human consumption both at home and abroad.

Information directly relevant to the control of FBT infections is to be found in publications by WHO, Technical Report Series No 849 (1) and by Lima dos Santos (21). Publications concerned with the prevention and control of schistosomiasis and soil-transmitted helminthiasis contain considerable relevant detail about the steps involved in planning, implementing and monitoring control programmes (22, 23).

There is no control blueprint which can be applied to FBT infections wherever they exist. Knowledge of local circumstances including cultural traditions, socio-economic factors, geography, infrastructure, climate, water resources and the distribution and population biology of all types of host in the trematodes' life cycles will need to be obtained before control programmes are planned and implemented. Also, a thorough assessment must be made of the resources available to run, manage and sustain the chosen control strategy. Do systems exist for drug procurement and distribution? Are enough staff available to carry out the required epidemiological and diagnostic work? Are staff (managers, technicians, educators, health workers) properly trained for their duties? Has the budget been prepared with sufficient detail

and with a contingency element? Since intersectoral collaboration is now recognized as essential for successful parasite control, have procedures for collaboration, communication and financial management been negotiated and agreed from the outset?

2.2.1 Epidemiology

Accurate quantitative information is needed about the distribution and abundance of the infections of interest. If not already available, this information must be obtained to ensure realistic planning, appropriate implementation, efficient management of resources and reliable monitoring. Examples of how to plan and conduct epidemiological surveys are described by Montresor *et al.*, (22). Although the Montresor guidelines were developed for the control of schistosomiasis and soil-transmitted helminthiasis, they illustrate the degree of detail that must be considered when embarking on helminth control programmes.

2.2.2 Access to treatment

Treatment to relieve infected individuals from the burden of disease depends on ensuring access to secure diagnosis and essential drugs in all health systems in all areas where FBT infections are endemic. This conclusion implies the improvement of the capacity of the primary health care system in case detection and in the provision of proper treatment. These basic public health measures will not only reduce morbidity but will also lead to a reduction in the number of eggs being released into the environment. Campaigns involving either the universal, targeted or selective administration of anthelmintic drugs to communities may be judged to be necessary based on the results of epidemiological surveys, community pressure and clinical reports.

Diagnosis

Diagnosis based on finding and identifying trematode eggs in stools is not straightforward, given the numbers of species involved and the similarity of the eggs of many of them (Section 3.4). From a public health perspective, inability to identify trematode species based on finding their eggs need not be considered a reason for withholding anthelmintic treatment from individuals or communities. Fortunately, in cases where accurate parasitological diagnosis is difficult, the important step is to establish the presence of a FBT infection because praziquantel (PZQ), the anthelmintic drug of choice in such cases, has broad applicability.

Clinical diagnosis may be unreliable if trematode eggs cannot be detected in the stools or sputum of suspected cases. Unless health workers have undergone extensive training, the risk of misdiagnosis (Section 3.4) will remain. Serodiagnostic procedures and non-invasive methods such as ultrasonography can be used to improve the prospects of accurate diagnosis (10; Annex 3).

Anthelmintic chemotherapy

PZQ (24) is the drug of choice for the treatment of infection with most species of FBTs. The mode of action of PZQ is not fully understood but it rapidly causes tegumental damage and paralytic muscular contraction of adult trematodes leading to their death and elimination. Full details of the pharmacokinetics and other properties of PZQ have been reviewed recently by a WHO Informal Consultation (25). PZQ is exceptionally well tolerated although side effects such as abdominal discomfort, nausea, headache and dizziness may be experienced by some patients. Treatment of hamsters with PZQ to expel *O. viverrini* has been found to reduce chronic proliferative cholangitis, a precancerous stage in the development of cholangiocarcinoma (26).

Since the expiry of patents, good quality generic PZQ has become widely available costing about US\$ 0.065 per 600 mg tablet. PZQ is highly effective for the treatment of liver fluke infections, lung fluke infections and intestinal fluke infections including fasciolopsiasis. PZQ is not particularly effective in the treatment of fascioliasis.

Triclabendazole (TCZ) is a benzimidazole compound with selective action against immature and mature trematodes in mammalian hosts. TCZ has been used for treating fascioliasis in sheep and cattle since 1983. Triclabendazole is now available for human use and is recommended by WHO. Details of its properties have been described by Richter *et al.* (27).

The following extracts from the latest edition of the *WHO Model Formulary* (24) set out how PZQ and TCZ should be used for the treatment of FBT infections in humans:

2.3 Fluke infections ¹

Praziquantel

Tablets: Praziquantel 600 mg.

Uses: Intestinal flukes, liver flukes and lung flukes; cestode infections (Section 6.1.1.1); schistosomiasis (Section 6.1.3.1).

Contraindications: ocular cysticercosis (see Section 6.1.1.1).

Precautions: *Paragonimus* infections – treatment in hospital is recommended as there may be central nervous system involvement; pregnancy (unless immediate treatment required, delay treatment until after delivery); breast-feeding (avoid during and for 72 hours after treatment); areas endemic for cysticercosis – possible oedematous reaction.

Interactions: May impair ability to perform skilled tasks. For example operating machinery, driving.

Doses: Intestinal fluke infections, *by mouth*, adult and child over four years of age, 25 mg/kg as a single dose.

Liver and lung fluke infections, *by mouth*, adult and child over four years of age, 25 mg/kg three times a day for two consecutive days; alternatively 40 mg/kg as a single dose. Treatment may need to be extended for several days in paragonimiasis.

Adverse effects: abdominal discomfort, nausea, vomiting, malaise, headache, dizziness, drowsiness, rectal bleeding; rarely hypersensitivity reactions, including fever, and pruritus.

Triclabendazole

Tablets: Triclabendazole 250 mg.

Uses: fascioliasis; paragonimiasis.

¹ The sections cited in the extracts from the *WHO Model Formulary* (24) refer to sections in that publication and not in this report.

Precautions: *Paragonimus* infections – treatment in hospital is recommended as there may be central nervous system involvement; severe fascioliasis - biliary colic, due to obstruction by dying worms.

Dosage: Fascioliasis, *by mouth*, adult and child over four years of age, 10 mg/kg as a single dose. Paragonimiasis, *by mouth*, adult and child over four years of age, 20 mg/kg given in two divided doses.

Adverse effects: gastrointestinal discomfort; headache.

Managers of programmes designed to control FBT infections may wish to consider the development of a ‘tablet pole’ to facilitate calculation of the correct doses of PZQ and TCZ which must be given on the basis of individual body weight (see 23).

Recent research has proved that the genes conforming resistance to PZQ exist in schistosomes. There are no reports of PZQ resistance in FBT infections but the possibility of this problem should not be ignored. The development of new drugs for the control of FBT infections offers the most useful means of dealing with PZQ resistance. The wide scale use of TCZ among sheep and cattle has been accompanied by the emergence of populations of TCZ-resistant flukes in Europe.

2.3.1 Health education

Health education delivered in a culturally appropriate and socially acceptable manner is a foundation for the prevention and control of parasitic infection and disease. Health messages concerning FBT infections should focus on: (a) basic knowledge of the infections and their relationship to disease; (b) practical steps for reducing the risks of becoming infected; and (c) how to get treatment.

Accordingly, attention should be given to the following educational themes:

- FBTs are parasites which persist through a cycle involving freshwater snails, freshwater plants, crustaceans and fish with which humans make contact.
- Humans become infected when the microscopic parasites are eaten during meals involving raw or undercooked plants, crustaceans or fish.
- Domesticated and wild animals are also susceptible to infection with the same FBTs as those that infect humans.
- Infection with FBTs leads to diseases of the liver, lungs and gut.
- Risk of infection is reduced if freshwater plants, crustaceans and fish are properly cooked before being eaten.
- The risk of infection is reduced if the practice of adding fresh human and animal faeces is avoided.
- Individuals who know or suspect they are suffering from FBT infections should seek treatment from the nearest primary health care centre.

Such messages can be disseminated through schools, community organizations and all forms of the media (radio, television, newspapers, cinema). A strong health education campaign would be expected to make a significant but slow contribution to the prevention and control of FBT infection.

2.3.2 Sanitation

Good sanitation and hygiene are key for breaking the life cycle of parasites. Proper selection of the aquaculture site, the use of quality water and the training of workers to increase their knowledge and understanding regarding the routes of transmission of the parasites can reduce considerably the contamination of fish with parasites. However, these sanitary practices are not easy to implement in small scale subsistence fish farming situations. The traditional practices of building latrines above carp ponds and using nightsoil as fertilizer helps to maintain infections in cultured fish populations, while cultural practices of consuming raw or inadequately cooked fish products continue to keep infections in rural populations. Adopting a strategy of using livestock waste in fish culture has made important contributions to improving health and hygiene in various countries. In Taiwan, China, for example, economic growth with improved sanitation and increasing livestock production have led to replacement of human waste with pig and poultry manure as fertilizers in fish culture over the last few decades. However, there may be risks to human health through such practices (see 28). Particularly integrated livestock and fish systems with ducks efficiently controls the intermediate snail hosts and, thus, breaks the life cycle of the parasites. Another good management practice contributing to the biological control of the intermediate hosts is the stocking of mollusc-feeding fish species. Education and awareness building among communities on the benefits of adequate cooking and preparation of fish also help to reduce the disease risks.

2.3.3 Water management

The elimination of parasites or their intermediate snail hosts from the water in areas endemic for trematodiasis is difficult. Wherever possible, the water safety should be checked and, if needed, the water can be treated to prevent fish contamination with parasites. However, this is very difficult to implement in many developing countries, especially by low-income fish farmers.

2.3.4 Good agricultural/aquaculture practices

Good aquaculture practices are those practices adopted by fish farmers which are in accordance with the requirements for the production of safe and quality fish. They encompass the selection of the aquaculture site, water control and treatment, fish fry and fingerlings selection, feed control and hygienic practices. Again, these are possible in intensive, industrial aquaculture practices but are very difficult to implement in small-scale subsistence fish farming situations.

2.3.5 Food safety measures

Several techniques can eliminate the risk of FBTs from fish. These include freezing (e.g. at -20°C for 7 days) or heat treatment (e.g. cooking) can eliminate the risk of FBTs. Implementation of Hazard Analysis Critical Control Point (HACCP)-based systems have also achieved satisfactory results for FBTs control in several countries. Again, these safety measures can be very difficult to implement in small-scale subsistence aquaculture situations. Education and awareness building among communities on the benefits of adequate cooking and preparation can be the most efficient FBTs control measures.

2.3.6 Overview

Anthelmintic chemotherapy when used at the public health level in response to epidemiological information or on a case-by-case basis can serve to reduce and control morbidity due to FBT infections. However, high rates of re-infection are to be expected following chemotherapy, so sustaining the achievements of chemotherapy and progressing towards prevention and longer term control will require a broader, holistic approach. The challenge to health posed by intermediate snail hosts can be addressed by clearing aquatic vegetation and improving the velocity of water-flow. If possible, reservoir hosts should be identified and treated. Reduction of contamination of fish ponds with faeces should be introduced. Food inspection routines should be developed and implemented. Health education to explain why all these measures are required should be an integral part of the prevention and control of FBT infections.

2.4 Practical strategies for the prevention and control of FBT infections in Asia

2.4.1 Public health measures for FBT control

The most realistic, practical starting point for the prevention and control of FBT infections in affected communities is to select a strategy that will enable morbidity to be reduced and then progress to be sustained. A model framework setting out an approach for achieving this objective is set out in Annex 4 and a critique of how to bring opisthorchiasis under control is provided (see 29).

2.4.2 Aquaculture measures for FBT control

There is little published information about FBT control in aquaculture systems although avoidance of the use of contaminated faeces in fish ponds is important (see section 6.4). A pilot project based on the HACCP concept (1, 21) and carried out in Thailand provided a framework for the prevention and control of *O. viverrini* infection in carp cultivated in ponds (30). This test of the HACCP concept showed that a multidisciplinary strategy can be used to cover all aspects of fish rearing and consumption. Guidelines for the control of *C. sinensis* under conditions of aquaculture in China have been published by Li *et al.* (31). They advise the annual decontamination of fish ponds to destroy intermediate hosts, excrement management and regular anthelmintic chemotherapy for the local population. There would appear to be an urgent need to conduct operational research on the prevention and control of FBT infections under actual aquaculture conditions.

2.5 Intersectoral negotiation and collaboration

The need for practical intersectoral collaboration was emphasized by the WHO Study Group at the Manila meeting in October 1993 (1) and recognition of the importance of such collaboration is apparent from the Opening Addresses which introduce the current report. The participation of Ministers of Health and of Agriculture from the same government and of representatives of different United Nations agencies testifies to the role that intersectoral collaboration is required to play in the prevention and control of FBT infections.

FBT infections are intimately linked to the contact that humans have with fresh water and the development of this precious resource. The use and development of water resources is essential for all levels of aquaculture. Successful intersectoral collaboration between government ministries, industry, universities, environmental agencies, the media and other institutions will greatly increase the likelihood of preventing and controlling FBT infections.

Intersectoral collaboration does not happen quickly. It requires a detailed analysis of the issues of concern to each player followed by negotiation to agree the responsibilities and remits of each partner. Hunter *et al.* (32) published a framework showing how measures to manage parasitic disease can be built into projects designed to develop water resources. The subtitle of this publication is '*The need for intersectoral negotiation*' and a section is devoted to this theme. Freshwater aquaculture is also discussed. It is recommended that officials planning FBT control consult this comprehensive report by Hunter *et al.* (32).

2.6 Integration of FBT control with existing programmes

Experience has shown that the resources required to support vertical programmes dedicated to the control of particular parasitic infections are usually greater than the amount available in the public health budget. Experience has also shown that control programmes can be run efficiently and more cost-effectively if they are integrated with existing programmes (e.g. nutrition; lymphatic filariasis; immunization) or included in new initiatives. This integrated approach enables savings to be made in transport, technical time, administration, etc. Opportunities for the integration of FBT control with other public health programmes will depend on the priorities, resources and policies of governments in countries where FBT infections are endemic. The success of integrated prevention and control measures will largely depend on the willingness to collaborate intersectorally.

2.7 Experience of FBT prevention and control in Asian countries

Actions to prevent and control FBT infections have been taken and are continuing in China, Japan, Lao People's Democratic Republic, Philippines, Republic of Korea, Thailand and Viet Nam. The form and extent of the actions taken in the different countries is varied; resources, public health priorities and other factors determine the nature of the response to FBT control (1).

The national control programme adopted and sustained in Thailand provides an example of how to proceed and reveals that FBT control cannot be achieved overnight. Key features in the chronology of the programme are as follows:

- 1950: control began
- 1958-1967: integration of FBT control with the Rural Health Development Project
- 1974-1980: extensive health education provided through the rural health service
- 1980-1983: field trials with PZQ for treatment of liver fluke infections (*O. viverrini*); cure rate of 95%
- 1983-1987: liver fluke treatment unit established, > 400 000 cases treated
- 1987-1992: liver fluke control included in the National Public Health Development Plan, c. 1 800 000 cases treated

In addition, the Thai-German Liver Fluke Control Project was established in 1989 providing technical support, model development, management systems, evaluation protocols and technical staff training. Since 1992, liver fluke control has been extended and now operates in all the northern and some central provinces of Thailand, 42 provinces in total.

A conceptual framework identifying the main elements for large-scale FBT control at the public health level is provided by Annex 5. This scheme represents a modification of that developed for the control of liver fluke in Thailand by the Bureau of General Communicable Disease, Ministry of Health, Thailand. Self-reliance is identified in the conceptual framework (Annex 5) as an important element of FBT control because it contributes significantly to sustainable control following the early progress. The strategy adopted for self-reliance in Thailand's liver fluke control programme is illustrated in Annex 6.

The experience from Thailand and elsewhere demonstrates that progress can be made in controlling FBT infections given political will, community compliance and well managed resources. Statistics dealing with the diagnosis and treatment of *O. viverrini* infections in Thailand strongly support that conclusion (Table 3).

Table 3. Impact of control measures directed at liver fluke (*Opisthorchis viverrini*) infections in Thailand

Year	No. of stools examined	No. of stools positive for liver fluke	Prevalence (%)	No. treated
1984-87	629 522	400 452	63	400 452
1989	1 343 110	407 309	30	373 843
1996	3 007 125	356 010	12	364 975
2000	1 448 877	97 419	7	95 393

Note: Data abstracted from figures supplied by the Ministry of Health, Thailand)

2.8 Research topics related to the prevention and control of FBT infections

2.8.1 Treatment and control

Investigate the proposed relationship between FBT-induced morbidity and the intensity of infection. An understanding of the relationship between infection intensity, multiple species infection and morbidity is particularly needed for infection with heterophyids and gnathastomes.

- Measure the reversal and remission in FBT-induced pathology following anthelmintic treatment.
- Examine and compare the cost-effectiveness of the different treatment strategies (universal, targeted, selective and treatment based on self-diagnosis) employing anthelmintic drugs for control of FBTs.
- Research and development of effective molluscides in the context of current concern over ecotoxicology.

2.8.2 Diagnosis

- Develop and test, under field and clinical conditions as appropriate, methods to improve the reliability of diagnosis of FBT infections in both humans and domesticated animals (reservoir hosts). Research should include: (a) differential

staining of FBT eggs; (b) PCR probes for FBT eggs; (c) coproantigen and circular antigen assays; and (4) serum immunodiagnostic assays.

- Develop improved techniques for the reliable identification of cercariae and metacercariae to strengthen epidemiological and monitoring surveys.

2.8.3 Risk assessment

- Investigate quantitatively the relative contributions of human and reservoir hosts to the contamination of the environment (freshwater harbouring invertebrates, fish and plants required for FBT life cycles).
- Investigate FBT transmission dynamics, including seasonal effects, under varying conditions of aquaculture.
- Examine the possibilities for and consequences of the selection and genetic manipulation of food fish species with a view to obtaining stock resistant to FBT infection.
- Construct a mathematical framework to model FBT transmission under a range of conditions thereby identifying opportunities for the implementation of control measures.

2.8.4 Quality control of aquaculture products

- Develop and test methods for neutralizing metacercariae on or in freshwater aquaculture products without introducing or passing on health risk factors to consumers.
- Prepare a code of practice, based on the HACCP concept, that must be followed to ensure that freshwater aquaculture products are safe for human consumption with respect to FBT infections.
- Establish protocols for checking the FBT infection status of fish fry before their distribution.

3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Policy issues

- Governments of countries where FBT infections occur should ensure access to essential drugs for the treatment of these infections in all health systems in all endemic areas. Given the involvement of *O. viverrini* and *C. sinensis* in cholangiocarcinoma and the difficulties encountered in the early diagnosis of this malignancy, it is imperative that access to anthelmintic treatment be available for all people living where these infections are known to be or are found to be endemic.
- Governments should take immediate steps to register triclabendazole for use in their countries.

- Governments of countries where FBT infections occur should authorize the design and implementation of national control programmes for FBT infections if these do not already exist.
- Each government should establish an intersectoral working group to ensure efficient and effective measures for FBT prevention and control.
- Governments should integrate FBT control programmes into existing primary health care systems and continue active surveillance and treatment in all endemic areas.
- Health education, sanitation and safe waste disposal should be promoted as important elements in FBT control.
- Governments with overall responsibility for a commercial freshwater aquaculture industry should establish and legislate for best practice for eliminating the risk of FBT infection from aquaculture systems and products.

3.2 Technical issues

- The research-based pharmaceutical industry should be urged to develop and market new drugs to extend the choice available for the treatment of *Opisthorchis viverrini*, *Clonorchis sinensis* and intestinal flukes and so provide options for dealing with drug resistance.
- Where needed, guidelines for designing and implementing epidemiological surveys should be prepared in order to obtain accurate and reliable information about the distribution and abundance of FBT infections.
- Methods should be developed for the detection, monitoring and prevention of the emergence of drug resistance in FBTs.
- Training sessions should be established for health workers with the objective of improving diagnostic quality and reducing the occurrence of misdiagnosis.
- Surveillance for pulmonary tuberculosis should be integrated with surveillance for paragonimiasis.
- Health education messages should be prepared and disseminated to inform people about the risks of becoming infected with FBTs through eating raw freshwater fish, crustaceans and plants.
- Health education messages should be prepared and disseminated to inform people about the risks of maintaining and spreading FBT infections if untreated human and animal faeces are allowed to contaminate freshwater ponds where fish are cultured.

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GLOSSARY OF KEY TERMS AND ABBREVIATIONS

Billion

A thousand million

CC

Cholangiocellular carcinoma

Cholangiocarcinoma (cholangiocellular carcinoma)

A malignant tumour arising in the liver from the bile duct epithelium.

community

A group of people living in a particular area or ecological zone.

cure rate (CR)

The number (usually expressed as a percentage) of subjects found to be egg negative on examination of a stool or urine sample using a standard procedure at a set time after deworming.

DMN

Dimethylnitrosamine

drug resistance

A genetically transmitted loss of sensitivity for a drug in a worm population which was previously sensitive to the appropriate therapeutic dose.

ecological zone

A zone reflects the tolerance of the worm species in question (or its intermediate host) of ecological and variables such as topography, soil type, altitude (temperature), rainfall or frost. The zonation delineated in this way may vary from one country to another.

effectiveness

A measure of the effect of a drug against a worm infection under operational conditions.

efficacy

A measure of the effect of a drug against a worm infection in isolation under ideal conditions.

Egg reduction rate (ERR)

The percentage fall in egg counts after deworming based on examination of stool or urine sample using a standard procedure at a set time after the treatment.

ELISA

Enzyme-linked immunosorbent assay

environmental management

The planning, organization, carrying out and monitoring of activities for the modification and/or manipulation of environmental factors or their interaction with humans with a view to preventing or minimizing vector propagation and reducing man-vector-pathogen contact.

environmental manipulation

A form of environmental management consisting of any planned recurrent activity aimed at producing temporary conditions unfavourable to breeding of vectors in their habitats.

environmental modification

A form of environmental management consisting of any physical transformation that is permanent or long-lasting of land, water and vegetation, aimed at preventing, eliminating or reducing the habitats of vector without causing unduly adverse effects on the quality of the human environment.

eosinophilia

The formation and accumulation of a significantly higher than normal number of eosinophils in the blood.

FAA

N-2-fluorenylacetamide

FAO

Food and Agriculture Organization

FBT

Food-borne trematode

HACCP

Hazard analysis critical control point.

haemoptysis

The expectoration of blood or blood-stained sputum.

host (for FBTs)

- Intermediate: a species of host in which the FBT is known or is assumed to develop but in which sexual maturity is not attained.
- Definitive: a species of host in which the FBT attains sexual maturity.
- Reservoir: a non-human definitive host.

incidence

The number (usually expressed as percentage) of new cases of infection appearing in a population in a given period of time.

intensity

The number of worms (measured directly or indirectly) per infected person (worm burden).

metacercaria

An encysted stage of a fluke necessary for the transmission and establishment of infection in a definitive host.

metric ton (tonne)

1000 kilograms

morbidity

Clinical consequences of infections and diseases that affect an individual's well-being.

morbidity control

Avoidance of illness caused by heavy intensity worm infections. It is obtained by periodically lowering the worm load in individuals and groups known to harbour heavy intensity infections.

ppm

Parts per million

prevalence

The number (usually expressed as percentage) of individuals in a population estimated to be infected with a particular species of worm.

PZQ

Praziquantel

risk group

Those identified to be at risk of morbidity and mortality as a result of infection with schistosomes and soil-transmitted helminths. Such groups include pre-school children, school-age children, pregnant women and workers with occupations involving contact with fresh water.

sanitation sensu lato or environmental sanitation

Intervention to reduce environmental health risk that includes the safe disposal of hygienic management of human and animal excreta, refuse and wastewater; the control of vector, intermediate host and reservoirs of disease; the provision of safe drinking water; food safety; the provision of adequate housing in terms of location, quality of shelter and indoor living conditions; the provision of facilities for personal and domestic hygiene; and the provision of safe and healthy working conditions.

sanitation sensu strictu

The provision of access to adequate facilities for the safe disposal of human excreta, particularly aimed at vulnerable groups and usually combined with the provision of access to safe drinking water.

TCZ

Triclabendazole

treatment strategies

1. *Selective*: individual level deworming where selection for treatment is based on a diagnosis of infection, an assessment of the intensity of infection, or based on presumptive grounds. This strategy can be used in whole populations or in defined risk groups.
2. *Targeted*: group level deworming where the (risk) group to be treated (without prior diagnosis) may be defined by age, gender or other social characteristics, irrespective of infection status.
3. *Universal*: population level deworming in which the community is treated irrespective of age, gender, infection status or other social characteristics.

WHO

World Health Organization

zoonosis

Disease of animals transmissible to humans.

**INFORMATION PRESENTED AT THE FBT WORKSHOP,
HA NOI, VIET NAM (NOVEMBER 2002) ABOUT THE DISTRIBUTION AND
ABUNDANCE OF HUMAN FBT INFECTIONS IN ASIA**

CHINA

A national survey on the current status of major human parasitic diseases in China is underway. Members of the Workshop were advised that the following numbers of infections might be found to be inaccurate. Updated information will be available after the current national survey is completed. Overall, FBT infections probably occur to some extent in 25 of China's provinces, municipalities and autonomous regions.

- *Clonorchis sinensis* - 10 million infections
- *Fasciola gigantica*
- *Fasciola hepatica/Fasciolopsis buski* - 160 000 infections/200 000 infections
- *Paragonimus spp.* <1 million infections
- Other species of intestinal FBT - 380 000 infections

JAPAN

- *Metagonimus yokogawai* - 150 000 infections
- *Paragonimus spp.*- 50-100 infections reported annually

LAO PEOPLE'S DEMOCRATIC REPUBLIC

Opisthorchis viverrini - 2 million infections; 24% prevalence in southern provinces; 48% prevalence in school children.

PHILIPPINES

Twenty-one species of heterophyid trematodes reported in the Philippines, generally with low prevalence rates. The prevalence of heterophyid infections on Mindanao Island found to be 36%. *Haplorchis taichui* may be the commonest infection.

SOUTH KOREA

- *Clonorchis sinensis* - 700 000 infections
- *Metagonimus yokogawai* - 300 000 infections
- *Paragonimus spp.* - 1 000 infections
- Other species of intestinal FBT - 257 infections

THAILAND

- *Fasciolopsis buski* - 10 000 infections
- *Opisthorchis viverrini* - 19.3%, 15.7%, 3.8% and 0% prevalence in North, Northeast, Central and South Thailand, respectively; 8 million people infected

VIET NAM

- *Clonorchis/Opisthorchis* - 21% (0.2%-37%) in 15 states surveyed
- *Fasciola gigantica* - 700 infections since 1997 in central Viet Nam
- *Fasciolopsis buski* - low prevalence, widely distributed
- *Paragonimus* spp. - 0.2% - 15% prevalence in 8 provinces in northern Viet Nam

EXISTING MORBIDITY MARKERS FOR DISEASE DUE TO FBT INFECTIONS

1. Quantitative parasitological stool examination/sputum examination
2. Signs and symptoms
3. Haematology
4. Liver enzymes (alkaline phosphatase, gamma-GT, GPT)
5. Serology
6. Worm antigens (fascioliasis)
7. Ultrasound morphology
8. X-ray (lung flukes). Oro-cholecystography, CT-scan
9. Tumour markers
10. Autopsy data
11. Methods for detecting ectopic disease

Pro's and con's of each method

1. Parasitological stool examination

Multiple stool examinations (three or more) may be required.

Most sensitive technique for *Fasciola* spp. is the sedimentation (conic-cup sedimentation). Alternatively, Kato-Katz or enrichment methods may be used. Kato-Katz examinations allow quantification.

2. Signs and symptoms

There are no established key symptoms especially during early infections with *O. viverrini* and *C. sinensis*. Symptoms including unwellness, fatigue, post-prandial indigestion, recurrent dull abdominal post-prandial pain, and anorexia and relapsing cholangitis, usually occur in long established infections. Spontaneous limitation of physical activity. Hot cutaneous sensation over the upper abdomen (especially right-sided) or back. Palpable gallbladder. Painless slowly progressing jaundice (Courvoisier sign) in cholangiocarcinoma.

Fasciola spp: Clinical signs and symptoms include: (a) knowledge of source of infection, areas of endemicity or repeated epidemic outbreaks, risk behaviour, clustering of infection and time elapsed after infection are useful diagnostic clues; and (b) suspicious symptoms (fever, asthenia) in the acute stage. In chronic stage, (biliary colics, anorexia) non-specific or lacking (latent disease).

Paragonimus spp: Clinical signs and symptoms include exertional blood coughing, suspected chemo-resistant tuberculosis, and characteristic rusty sputum (different from hemoptysis present in tuberculosis).

3. Eosinophilia

Usually high during acute infection by *Fasciola* spp. and *Paragonimus* spp. In multiple helminthic infections and allergies, Eosinophilia also occurs so that in most endemic countries eosinophilia is non-specific.

4. Liver enzymes

Easy to obtain results at a hospital level but difficult under rural conditions.

5. Serology

Antibodies may not be detectable in the very early stage of an infection and they may persist for a rather long time after elimination of the flukes. Serology is not suitable for short-term monitoring of infections and is too expensive for public health services in many endemic areas.

6. Worm antigens

Fasciola-secretory-excretory antibodies are detectable in serum during the acute stage and in faeces during the chronic stage of an infection. However, false negative results may occur (<15%). Antigen detection is useful for monitoring (decrease after successful treatment) but the technique is expensive.

7. Ultrasonography (X-ray, where not available)

Useful for diagnosis of organ involvement in acute and chronic stages and for diagnosis of complications (pneumothorax, ascites, worms, sludge and stones in gall bladder, sonographic Murphy+, decreased post-prandial gb-contraction (<50%), bile duct dilation, - contents). Not sufficiently sensitive for detecting parasites. Useful for the quantification of biliary abnormalities and exploring the suspicion of cholangiocarcinoma.

8. X-ray (see Ultrasonography)

9. Tumour markers

CEA and Ca 19/9 may be positive in cases of cholangiocarcinoma if markers are excreted in blood. Proof of cholangiocarcinoma based solely on histological examination is usually not cost effective and may not prove presence of cholangiocarcinoma.

10. Autopsy data

Cholangiocarcinoma is rapidly fatal. Autopsy studies permit the verification of the condition and differential diagnosis from hepatocellular carcinoma. Ensure autopsy is culturally accepted by people in the endemic area of interest.

11. Methods for detecting ectopic sites

Ectopic localisations may require different diagnostic means. Especially dangerous cerebral localizations may require CT-imaging. These may also cause problems during treatment (e.g. seizures). Ultrasound and X-ray may also be useful in diagnosing these conditions.

A MODEL FRAMEWORK FOR THE GUIDANCE OF PUBLIC HEALTH WORKERS RESPONSIBLE FOR CONTROLLING MORBIDITY DUE TO FBT INFECTIONS

1. Priority actions

- 1.1 Assessment of priorities and selections of cost-effective interventions.
 - Cost of disease burden.
 - Cost of treatment and prevention.
- 1.2 The demographic, epidemiologic and economic information produced should be used for planning and strategy selection.
- 1.3 Needs assessment: rapid epidemiological evaluation and choice of appropriate interventions
 - Felt needs of the community.
 - Types of infection present and their distribution and abundance (importantly, check health centre records and other sources for data on positive cases).
 - Extent and severity of morbidity.
 - Availability and accessibility of primary health care.
 - Nature of the environment and ecological features.
 - Situation regarding intersectoral collaboration.
 - Situation regarding sanitation.
 - Levels of managerial and technical support.
 - Staff training.

2. Control of FBT

- 2.1 Praziquantel has been found to be highly efficacious but treatment is only part of the answer to the control of this disease.
- 2.2 The control of the intermediate host is not a practical option because in many countries freshwater fish is the staple diet and is imported from many locations. (Snail control is also not practical since it is expensive and there is great danger in upsetting aquatic environments.)
- 2.3 Some success has been met using epidemiological approaches. These are implemented at the level of community health but is difficult to change strongly embedded cultural practices which include the eating of uncooked fish.
- 2.4 Measures such as education, the provision of better sanitation and annual drug treatment have had some measure of success.

3. FBT control: set the targets

- 3.1 Reduce the prevalence and intensity of FBT infection?
- 3.2 Elimination of reservoir?
- 3.3 Interrupt the transmission?
- 3.4 Changing behaviour?
- 3.5 Disease control?

4. Disease control

- 4.1 Satisfactory resolution of morbidity is observed after treatment, as shown by significant clinical improvement, normalization of laboratory parameters and downgrading of the frequency of ultrasonographic abnormalities.
- 4.2 Strong evidence of a close relationship between *Opisthorchis* infection and human cholangiocarcinoma derives from both case-control studies and epidemiological surveys.

5. Disease control strategies

- 5.1 Universal drug administration.
- 5.2 Mass screening and treatment.
- 5.3 Passive case detection.
- 5.4 Information, education, communication.
- 5.5 Reduction of transmission.

6. Repeated universal drug administration

- 6.1 The recommended approach for other helminth infection control
- 6.2 Target groups are different in FBT
- 6.3 How long?
- 6.4 Impact on infection control
- 6.5 Typically donor dependant
- 6.6 Reduction in infection rate
- 6.7 Cost of delivery:
 - Training
 - Information campaigns
 - Drugs
- 6.8 Impact on morbidity

7. Mass screening and treatment

- 7.1 The strategy seems to be effective in reducing prevalence, intensity and morbidity.
- 7.2 Good impact on people awareness.
- 7.3 Highly demanding in human resources.

8. Passive case detection (PCD)

- 8.1 PCD is reported as a cost-effective intervention.
- 8.2 Positive interaction with primary health care.
- 8.3 'Socialization' of the disease control.
- 8.4 To be combined with health education.

9. Information, education, communication

9.1 What are the objectives?

- Changing behaviours
- Increasing awareness
- Creating needs
 - (a) Better health services
 - (b) Sanitation

10. Anthelmintic drugs

10.2 Price and quality

- Drug availability depended almost entirely on the level and duration of external donor support.
- With the expiry of patents, generic versions of anthelmintic drugs are now available at low cost. Praziquantel is now available as low as US\$ 0.065 per tablet.
- Drug quality control. There may be variations not only in content (amount of active ingredient) but also in purity, disintegration, dissolution and bio-availability, affecting the therapeutic value.
- Health managers should check the quality of the drug produced or obtained and avoid supplies of fake or counterfeit drugs. This is best done through an independent analysis.

10.2 Access

- In its essential medicine strategy, WHO has defined four key elements leading to good access to drugs:
 - (a) Affordable prices
 - (b) Reliable supply systems
 - (c) Sustainable financing
 - (d) Rational selection and use of drugs
- At the current price level of anthelmintic drugs, there may still be a need for donor support in helminth control, particularly in school-based or community-based interventions in the poorest sections of developing countries.
- However, due to the decrease in drug price, the cost-benefit ratio and the 'value for money' dimension of helminth control have significantly improved.

- Rational selection and use should not be underestimated in the quest for good access to drugs.
- A better implementation of symptom-based diagnosis for food-borne trematode infections at most peripheral health care levels can substantially improve access to treatment for those most in need. This could increase treatment compliance and lower the cost of treatment for the patient by 5 to 7-fold.
- Is the targeted treatment of high-risk groups the most rational approach to offer optimal access to the beneficial effects of treatment?

11. Strategies for morbidity reduction

11.1 Attack phase

- Mass stool examinations and selective treatment.

11.2 Consolidation phase

- Passive services operated at each level of the health system.

11.3 Cost of service delivery

Delivery systems for helminth control have often been dependent on vertical programmes.

- US\$ 0.51 per treatment in communities in Montserrat, US\$ 0.32 per treatment in Nigeria and US\$ 0.21 per treatment in Tanzania.

11.4 The high costs of this approach, in addition to concerns of ‘sustainability’, led workers to suggest integrated approaches capitalizing on existing infrastructure.

11.5 This approach has demonstrated that the cost of delivery of treatment targeted in this way could be as little as US\$ 0.03 per child treated.

11.6 Operational research has also established simple costing menus to illustrate the type of resources and cash expenditures needed to undertake the delivery of the drug in a school-based programme with albendazole or mebendazole and praziquantel.

11.7 The delivery cost

- Cost recovery
 - (a) Would people be willing to pay for or contribute to the costs of treatment?
 - (b) In many countries the expected answer might well be ‘no’ but reliable evidence to substantiate this preconception is limited.
 - (c) There could be opportunities to propose cost sharing.

11.8 Cost effectiveness

- Economic models have suggested that population screening and treatment may be a cost-effective method of reducing morbidity associated with helminth infections.

12. Recommended control objectives and strategies

- 12.1 Morbidity control as the first objective.
- 12.2 Ensuring access to essential drugs in all health facilities and by regularly treating groups which are at risk of developing morbidity.
- 12.3 Where community-wide treatment has achieved low prevalence of infection (with massive decreases in morbidity) the effort must be sustained and a more sustainable consolidation phase should be established.
- 12.4 In all cases and particularly where a permanent solution is aimed for, the strategy must be complemented by improved sanitation, hygiene in aquaculture and appropriate health education (and perhaps snail control measures) are required.

13. Assessment

- 13.1 All the suspected endemic provinces/districts should be evaluated.
- 13.2 In each province the number of endemic communes should be estimated, as well as the number of risk population and infected population (according to the result of the more recent surveys).
- 13.3 A map of the province indicating the endemic communes should be produced.
- 13.4 The availability of microscopes and microscopist should also be mapped.
- 13.5 The burden should be estimated based on:
 - (a) Records from district and provincial hospitals.
 - (b) Surveys using morbidity indicators.

14. Information – education

- 14.1 Eating raw fish is associated with a severe liver disease.
- 14.2 This disease could lead to liver cancer.
- 14.3 People should not defecate in the fishponds.
- 14.4 Fish should be cooked properly to protect from infection.
- 14.5 Diagnosis is easy, treatment is safe and effective.
- 14.6 Symptoms are: diarrhoea, flatulence, fatty-food intolerance, epigastric and right upper quadrant pain, jaundice, fever, hepatomegaly, lassitude, anorexia, emaciation, and oedema.
- 14.7 Latrines should be separated from fish ponds.
- 14.8 Cook the fish.
- 14.9 If eating raw fish, it is better to be periodically checked, at least once per year. Go to the health centre with a stool sample.
- 14.10 If one has symptoms of a suspected disease, they should be tested and treated.

15. Training

- 15.1 Health staff in all the primary health care stations in endemic areas should be able to suspect the disease, to identify trematode eggs with the microscopic examination of a stool sample and to properly treat both the infection and the clinical manifestation.

16. Access to diagnosis and treatment

- 16.1 All the health stations in high endemic areas should be equipped with a microscope, some basic material for stool examination (Kato method), a trained microscopist and praziquantel.

17. Measuring effects of control

- 17.1 Effect on disease and morbidity via clinical surveillance.
 - Ultrasounds indication of disease in liver?
 - Organomegaly?
 - Other indicators?
- 17.2 Effect on indices of infection.
- 17.3 Effect on human behaviour.
 - Contamination measured by infection rate in wild and/or sentinel snail.

18. Sustainability

- 18.1 Integration of control in existing structures and public health interventions, such as school health packages, together with decentralization of decision-making and delivery, are essential in high prevalence areas to ensure commitment and sustainability.
- 18.2 Health authorities must recognize FBT control as an integral part of primary health care services.

19. Conclusions

- 19.1 The choice of any strategy will ultimately depend on the cost-effectiveness ratio (cost per unit of effectiveness achieved) and existing budget constraints.
- 19.2 The cost-effectiveness ratio may in turn be affected by a wide variety of economic, epidemiological, demographic, technical and behavioural factors.
- 19.3 A comparative analysis of the cost-effectiveness of treatment should be completed based on parasitological and symptomatic screening.

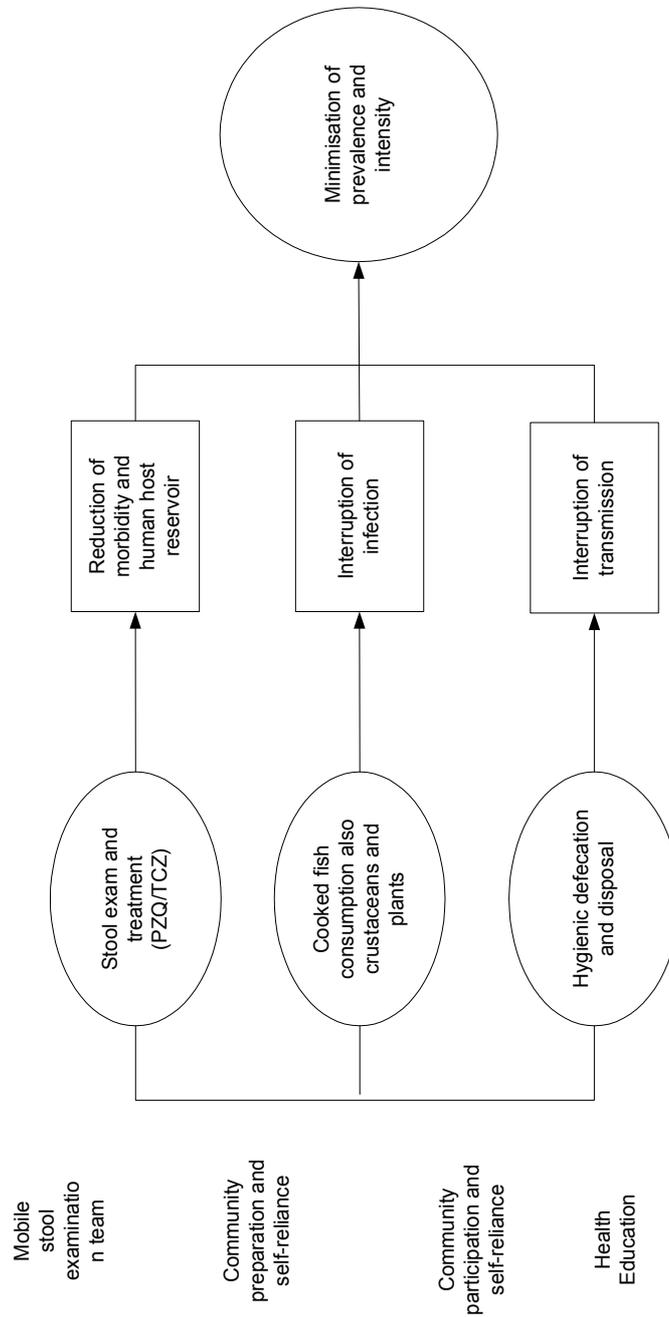
Note: Helpful information is available in the following publications which are available from WHO.

Montresor, A., Crompton, D.W.T., Gyorkos, T.W. and Savioli, L., 2002. *Helminth Control in School-age Children: A Guide for Managers of Control Programmes*. Geneva, World Health Organization.

WHO, 1995. *Control of foodborne trematode infections*. Report of a WHO Study Group. Geneva, World Health Organization.

WHO, 2002. *Prevention and control of schistosomiasis and soil-transmitted helminthiasis*. (Technical Report Series 912). Geneva, World Health Organization.

CONCEPTUAL FRAMEWORK FOR FBT CONTROL



OPENING ADDRESSES

Mrs Pascale Brudon

WHO Representative in Viet Nam

I am pleased to welcome you to this Joint WHO/FAO Regional Workshop on Foodborne Trematode Infections in Asia. I welcome this opportunity for WHO to collaborate with FAO in tackling this major public health problem.

Despite years of research and numerous control efforts, parasitic infections continue to be a major source of morbidity and mortality in many countries of the Western Pacific Region. Most, if not all, parasitic diseases are both preventable and treatable. However, despite this, the World Health Report 2000 reported that infectious and parasitic diseases remain the primary causes of death worldwide.

Parasitic diseases are neglected diseases that affect primarily the disadvantaged and poor segments of society. There has been little interest in supporting research to develop new drugs or new control strategies. Similarly, many governments fail to recognize parasitic diseases as important public health problems and do little to control them, even though the drugs that we have to treat the infections are both safe and inexpensive.

Among the most neglected of the parasitic diseases are those caused by foodborne trematodes. More than 40 million people are infected worldwide by this group of parasites. Most are in Asia where transmission is associated with poor hygiene, improper waste management and the widespread habit of eating raw fish.

The economic impact of food-borne trematodes was recently estimated in Thailand to be US\$ 65 million in lost income per annum. This is in addition to US\$ 19.4 million that is the estimated cost of treating infected individuals.

Clonorchiasis is endemic in China, Hong Kong (China), Japan, the Republic of Korea and Viet Nam. More than half of the seven million people infected are residing in China.

More than 10 million people suffer from *Opisthorchis* infection in the Lao People's Democratic Republic, Thailand and Viet Nam. In Thailand, 70% of the rural population living in the northeastern provinces has the infection, which is associated with cholangiocarcinoma, the most common form of liver cancer there.

Paragonimiasis is associated with certain species of freshwater crabs and crayfishes that are eaten raw. The disease, with TB-like clinical manifestations, affects 22 million persons in at least 20 countries, especially children; the major foci are in Asia.

Another emerging parasitic disease is caused by infection with *Fasciola*. This is associated with eating aquatic plants. The parasites are a public health problem in several South American and Middle Eastern countries. There are few data available about the parasite in Asia but clinical cases have been reported in several countries and the preliminary information from Viet Nam is alarming. For this disease there is no readily available treatment. The only effective drug is triclabendazole, which is not yet registered for human use in most of these endemic countries.

Most foodborne parasitic infections are associated with aquaculture products. Aquaculture is currently one of the fastest growing food production systems in the world. Approximately 90% of global aquaculture production is based in Asia. In the future, farmed fish will be an even more important source of protein foods than they are today and the safety for human consumption of products from aquaculture is of public health significance. The expansion of aquaculture could be associated with a further expansion of these infections.

The control of foodborne trematodes must be based on strong multisectoral cooperation. This is why WHO and FAO have decided to work together to encourage close collaboration between the health, agriculture and aquaculture sectors in all the endemic countries. These worms not only affect human health but they also slow down the economic development of endemic regions.

A strong political commitment to combating foodborne trematodes is also necessary. Governments need to mobilize resources and seek adequate strategies. When motivated health staff and public health managers are supported by political commitment, results are impressive and countries in this Region have provided a number of good examples already.

This workshop represents a milestone in our efforts to control foodborne trematodes. We have with us here today an outstanding group of international experts, government representatives from the most affected countries, as well as representatives from major academic and scientific institutions from around the world. Your job over the next three days is to produce a practical plan for the control of these parasites, taking into account the most effective and sustainable strategies that are currently available. I would like to stress the need for a practical approach that can be effectively applied in the most remote areas where the poor and most vulnerable groups live.

I would like to acknowledge the support of the Danish International Cooperation Agency, DANIDA and the Centre for Experimental Parasitology, our joint WHO and FAO Collaborating Centre for Emerging Parasitic Zoonoses in Denmark. They have helped us to make this meeting possible. I thank you for your participation and I wish you all a very productive meeting.

Dr Tran Thi Trung Chien
Minister of Health of Viet Nam

On behalf of the Ministry of Health of Viet Nam, I warmly welcome you all to this important workshop.

For more than a decade, the Government of Vietnam has attached high priority to infectious and parasitic disease control with the allocation of considerable resources and increased community mobilization. With support and guidance given by the people and the State, together with the great efforts of the health workers and close collaboration of other sectors and social organizations, Viet Nam has already gained remarkable achievements in polio eradication, control of TB, leprosy, malaria and other endemic diseases.

However, parasitic infections are still very common in Viet Nam. Contributing factors to the high infection rates include living conditions, low level of economic development, and poor environmental and sanitary conditions. In addition, several human behaviours contribute to the spreading of parasitic infections, such as the use of untreated nightsoil as a fertilizer in agriculture. Consumption of raw fish is common in some regions of Viet Nam and the low standard of procedures in domestic aquaculture are related to focal high endemic areas for foodborne trematodes.

Surveys carried out by the National Institute of Malariology, Parasitology and Entomology found that these infections are often highly prevalent. Twenty-six percent of the population was reported to be infected in Nam Dinh province and in Phu Yen, in the south of Viet Nam, 37% of people were found infected. Around five million people are exposed to the risk of infection by *Clonorchis sinensis* and *Opisthorchis viverrini* and around 400 000 to 500 000 are estimated to be infected. Most of those people who harbour the infection suffer a chronic biliary disease. Data from neighbouring countries show that infection with *O. viverrini* is associated with high incidence of liver cancer.

Paragonimiasis is a public health problem in some areas in the north of the country. In these areas the related pulmonary disease is common mainly in children and the symptoms often lead to an incorrect diagnosis of tuberculosis. *Fasciola* infection is a new emerging problem and alarming data have come from recent surveys.

Poverty is the cause of poor health, including disease due to parasitic infections. The Government of Viet Nam considers poverty reduction a high priority to support the country's socio-economic development. Together with the Comprehensive Poverty Reduction and Growth Strategy, the national targeted health programmes should contribute to alleviate the disease burden, particularly for the poor. In addition, the Government of Viet Nam is committed to strengthening and improving the grassroots health services. Recently, on 15 October 2002, the Prime Minister adopted Decision Number 139 regarding the Fund for Curative Health Care for the Poor. The establishment of this Fund with 75% financial contribution from the

State budget and 25% from mobilized sources will certainly improve the accessibility to curative health care by the poor and contribute to ensure equity in health care.

We are aware that inter-sectoral collaboration is the key to success in many health programmes. For worm control in school children, cooperation between the health and the education sectors is essential. In the control of foodborne trematodes, health and agriculture should join efforts and adopt a common agenda.

We are fully aware that the expertise and the enthusiasm of scientists, public health officers and health specialists need to be supported by a continued and strong political commitment. We are willing to support them. We hope that this meeting and your work will result in clear recommendations and in the identification of proper actions. This will assist us in Viet Nam to develop suitable policies and to adopt effective intervention strategies.

On this occasion, I would like to thank and welcome this joint initiative of FAO and WHO in holding this workshop in Viet Nam. I wish all of you good health and the workshop a great success.

Dr Ta Quang Ngoc

Minister of Fisheries of Viet Nam

On behalf of the Ministry of Fisheries of Viet Nam, I welcome all of our friends from many countries to Ha Noi to participate in the Joint WHO/FAO Workshop on Foodborne Trematode Infections in Asia.

The Ministry of Fisheries greatly appreciates the initiative of FAO and WHO to organize this workshop. The presence of leading experts in epidemiology, aquaculture, food processing and food safety from many international institutions and countries demonstrates that we are aware of and have the will to strengthen cooperation in communication and sharing experience in the prevention of foodborne trematode infections due to fish consumption.

Fishery products are a nutritious and healthy food and a favourite food of consumers worldwide. Fishery products are also a very important protein resource for the population and contribute to food security in many developing countries. That is why, in recent years, aquaculture in eastern and southern Asia has quickly developed. In Viet Nam, aquaculture production has grown steadily, representing a larger share of total fishery production. Aquaculture production provides a greater amount of raw material for processing for domestic consumption as well as a source of hard currency through export. The development of aquaculture has had a significant impact not only on the fisheries sector but also for economic development of rural areas. Jobs have been created and the income of farmers has improved according to policies of the Government in recent years to eradicate hunger and alleviate poverty.

More recently, in order to protect consumer health and satisfy the requirements of importing countries, the fishery sector has paid special attention to strengthening the control of hygiene and food safety conditions along the entire chain of fishery production 'from pond to table'. The control measures for public health hazards, including parasites in fish, have been set up and implemented at ponds, in fishing vessels, fishing ports, fish markets and handling and processing factories, according to international regulation standards on food hygiene and safety. Hence, the fishery products of Viet Nam have earned prestige for high quality and safety at many markets including those in countries with the strict requirements for food safety.

However, as well as providing nutritious food, fishery products could also put public health at risk if the hazards at harvesting and processing are inadequately controlled. Accordingly, measures applied in aquaculture practice for prevention of trematode infections in fish and control measures for eliminating trematode-infected fish at post-harvest handling and processing have been introduced in the fishery production chain. I would like hereby to express our thanks to international institutions (especially FAO and WHO) and all scientists in this country and abroad for giving help to the fishery sector in the implementation of the above mentioned effort.

This workshop is a good opportunity for discussion and exchange of opinions and for unification of cooperative efforts for proper control of foodborne trematode infections. I believe that through the workshop we will find useful measures as well as formulate plans for cooperation and communication in the future in order to achieve more effective control of trematode disease for consumers' health protection and sustainable aquaculture.

The Ministry of Fisheries expresses its wish for cooperation with WHO, FAO and all scientists, experts and managers in this country and abroad in setting up and implementation of Good Aquaculture Practice (GAP) in aquaculture for insuring food safety in general and the prevention of trematode infections in particular for consumers in the country and in importing countries. The Ministry of Fisheries is also willing to share experiences with other institutions and countries on this issue.

I wish all of the participants good health and a successful workshop.

Mr Jean-Francois Ghyoot
FAO Representative in Viet Nam

I am pleased to attend the opening of the WHO/FAO Foodborne Trematode Infections Workshop which is being held in collaboration with DANIDA, the Centre for Experimental Parasitology and the WHO/FAO Collaborating Centre for Emerging Parasitic Zoonoses.

Within the Asian region, the issue of fish-borne trematodes is receiving greater attention and focus. In March 1999 in Bangkok, FAO and SIFAR (Support Unit for International

Fisheries and Aquatic Research) jointly convened ‘The First Regional Workshop on Research into Prevention and Control of Human Fish-borne Trematode Infections’.

Foodborne trematodes are associated with aquaculture products. Aquaculture is currently one of the fastest growing food production systems in the world, with production increasing at an average rate of 9.6% per year over the past decade. Approximately 90% of global aquaculture production is based in Asia, where it provides an important source of dietary animal protein as well as income for millions of small-scale farmers in the region. In Viet Nam, four aquaculture projects are under implementation with support from FAO.

We understand that, while providing technical support to the development of aquaculture is essential, so also is introducing the means of prevention and control of related problems such as foodborne trematodes. The effective prevention and control can be achieved only with multi-sectoral efforts. That is the reason why WHO and FAO agreed in a joint initiative to hold a technical workshop.

It is a good time to hold this Regional Workshop to review the latest acquisitions three years after the first Regional Workshop and to discuss multi-sectoral approaches aimed at extending effective means of foodborne trematode control. Also, this workshop is a good example of constructive cooperation among UN agencies and among ministries. I hope the workshop will bring together all relevant and interested national institutions and ministries, donors and nongovernmental organizations and raise awareness on the topic and establish an effective communication network for all relevant organizations.

I would like to wish the workshop success and good health to all of you.

Mr Jordan Ryan

United Nations Coordinator in Viet Nam

I am pleased to welcome all of you to this Workshop on Foodborne Trematodes in Asia and I am particularly pleased that this is the result of a joint effort of two United Nations agencies: FAO and WHO.

Since the United Nations established its first representation in Viet Nam over 26 years ago, it has been combating poverty on many different fronts and in many different ways, through 13 resident agencies of the United Nations, all sharing a common goal: improving the lives of people in Viet Nam. Many achievements were recorded over the last years but many problems are still challenging our work. Among these problems, there are diseases of poor people, diseases that affect individuals and families, when the living conditions are poor and sanitation and health services lacking. Solutions exist and they are feasible and affordable but in order to reduce the burden of these ‘neglected’ diseases we need to join different expertise and

responsibilities. Foodborne trematode infections are an excellent example of these neglected diseases, where multi-sectoral cooperation is the most effective approach.

The United Nations advises and encourages governments to support inter-sectoral cooperation. There is growing convergence that by using a coordinated programme approach we enhance development effectiveness. In particular in the area of foodborne trematodes, parasites that constitute a relevant health hazard for large groups of population in Asia, the close collaboration among health, agriculture/aquaculture and veterinary services is crucial in order to bring remarkable and stable improvements. This inter-agency coordination effort enriches both its own activities and those of its partners in the pursuit of common goals. It also benefits the poor.

I think this partnership emphasizes the determination of the two agencies to implement their operations effectively. I hope and trust that the donors will also continue to support us and increase their support in material and financial terms.

The United Nations, in partnership with the government and people of Viet Nam, works to ensure that all Vietnamese people enjoy an increasingly healthy and prosperous life with greater human dignity and expanded choices. This action of WHO and FAO is another steps to help Viet Nam realize the Millennium Development Goals.

We wish this workshop great success.

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REFERENCES AND ADDITIONAL SOURCES OF INFORMATION FOR PUBLIC HEALTH WORKERS

1. Control of foodborne trematode infections. Report of a Who Study Group. Geneva, World Health Organization, 1995 (WHO Technical Report Series No 849).
2. Zaman, V. and Keong, L.A. Handbook of Medical Parasitology, 2nd Edition. Singapore, K C Ang Publishing Pte Ltd. 1989.
3. Coombs, I. and Crompton, D.W.T. A Guide to Human Helminths. London and Philadelphia, Taylor and Francis Ltd. 1991.
4. Chai, J-Y and Lee, S-H. Food-borne intestinal trematode infections in the Republic of Korea. *Parasitology International*, 2002, 51:129-154.
5. De N. et al. The foodborne trematode zoonoses of Vietnam. *Southeast Asian Journal of Tropical Medicine and Public Health*, 2003, 34, (Suppl. 1):12-34. 2003.
6. Rim, H-J. The current pathobiology and chemotherapy of clonorchiasis. *Korean Journal of Parsitology*, 1986, 24 (Suppl.):3-141.
7. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, Liver Flukes and *Helicobacter pylori*. Volume 61. Geneva, World Health Organization, 1994.
8. Haswell-Elkins, MR and Elkins, DB. Lung and liver flukes. In: Topley and Wilson's Microbiology and Microbial Infections, 9th edition, Volume 5, Parasitology. 1998. (eds. FEG Cox, JP Kreir and D. Wakelin). London, Arnold, pp 507-520.
9. Future use of new imaging technologies in developing countries. World Health Organization, 1985. (WHO Technical Report Series No 723. Geneva, World Health Organization, 1985.
10. Richter, J. et al. Fascioliasis: Sonographic abnormalities of the biliary tract and evolution after treatment with triclabendazole. *Tropical Medicine and International Health*, 1999, 4:774-781.
11. Okuda, K., Nakanuma, Y. and Miyazaki, M. Cholangiocarcinoma: Recent progress. *Journal of Gastroenterology and Hepatology*, 2002, 17:1049-1055.
12. Vatanasapt, V., Martin, N., Sriplung, H. et al. (Eds). Cancer in Thailand 1988-1991. International Agency for Research on Cancer. Technical Report 16. Lyon, France, 1993.
13. Watanapa, P. and Watanapa WB. Liver fluke-associated cholangiocarcinoma. *British Journal of Surgery*, 2002, 89:962-970.
14. Parkin, DM, Srivatanakul, P. and Khlatt, M. et al. Liver cancer in Thailand, I, a case-control study of cholangiocarcinoma. *International Journal of Cancer*, 1991, 48:323-328.
15. Iida H. Experimental study of the effects of *Chonorchis sinensis* infection on induction of cholangiocarcinoma in Syrian golden hamsters administered 0.03% N-2-fluorenylacetamide (FAA). *Japanese Journal of Parasitology*, 1985, 34:7-16.
16. Lee, J-H, Rim, H-J and Bak, U-B. Effect of *Clonorchis sinensis* infection and dimethylnitrosamine administration on the induction of cholangiocarcinoma in Syrian golden hamsters. *Korean Journal of Parasitology*, 1993, 31:21-30.
17. Lee, J-H, Yang, H-M and Bak, U-B. Promoting role of *Clonorchis sinensis* infection on induction of cholangiocarcinoma during two-step carcinogenesis. *Korean Journal of Parasitology*, 1994, 32:13-18.

18. Lee, J-H, Rim, H-J and Sell, S. Heterogeneity of the “oval cell” response in the hamster liver during cholangiocarcinogenesis following *Clonorchis sinensis* infection and dimethylnitrosamine treatment. *Journal of Hepatology*, 1997, 26:1313-1323.
19. Ditrich, O., Giboda, M. and Scholz, T. Comparative morphology of eggs of the Haplorchiinae (Trematoda: Heterophyidae) and some other medically important heterophyid and opisthorchid flukes. *Folia Parasitologia*, 1992, 32:123-132.
20. Bisseru, B. *Clonorchis sinensis* in West Malaysia. *Tropical and Geographical Medicine*, 1969, 33:352-256.
21. Lima dos Santos C. Hazard analysis critical control point and aquaculture. In: *Public, Animal and Environmental Aquaculture Health Issues*. (eds. ML Jahncke, ES Garrett, A. Reilly, RE Martin and E Cole). Chichester, Wiley-Interscience Inc. pp 103-119, 2002.
22. Montresor A et al. *Helminth control in school-age children: a guide for managers of control programmes*. Geneva. World Health Organization, 2002.
23. *Prevention and control of schistosomiasis and soil-transmitted helminthiasis*. Geneva, World Health Organization, 2002a (WHO Technical Report Series 912).
24. WHO model formulary. Geneva, World Health Organization. 2002b.
25. Report of the WHO Informal Consultation on the use of Praziquantel during pregnancy/lactation and albendazole/mebendazole in children under 24 months. Geneva, World Health Organization. 2003.
26. Thamavit, W., Moore, MA., Ruchirawat, S. Repeated exposure to *Opisthorchis viverrini* and treatment with the antihelminthic praziquantel lacks carcinogenic potential. *Carcinogenesis*, 1992, 13:309-11.
27. Richter, J. et al. Fascioliasis. *Current Treatment Options in Infectious Diseases*, 2002, 4:313-317.
28. Naegel, LCA. A review of public health problems associated with the integration of animal husbandry and aquaculture, with emphasis on Southeast Asia. *Biological Wastes*, 1990, 31: 69-83.
29. Hinz, E., Saowakontha, S. and Pipitgool, V. Opisthorchiasis control in Northeast Thailand: proposal for a new approach. *Applied Parasitology*, 1994, 35:118-124.
30. Khamboonruang, C., Keawvichit, R. and Wongwarapat, K., *South-East Asian Journal of Tropical Medicine and Public Health*, 1997, 28 (Suppl. 1):1164-1167.
31. Li, G., He, X. and Saidu, K. Epidemiology and control of clonorchiasis sinensis in China. *Southeast Asian Journal of Tropical Medicine and Public Health*, 2001, 32 (Suppl. 2):8-11.
32. Hunter, JM, Rey, L. and Chu, KY. Parasitic diseases in water resource development. The need for intersectoral negotiation. Geneva, World Health Organization, 1993.
33. Rim, H-J. Epidemiology and control of Clonorchiasis in Korea. *Southeast Asian Journal of Tropical Medicine and Public Health*, 1997, 28:47-50.
34. Giboda, M., Ditrich, O., Scholz, T., Viengsay, T. and Bouaphanh, S. Human *Opisthorchis* and *Haplorchis* infections in Laos. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1991, 85:538-540.

