MINI-REVIEW

Review and Current Status of *Opisthorchis viverrini* Infection at the Community Level in Thailand

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Abstract

***Opisthorchis viverrini* is remains a public health problem in Thailand, particularly in the northeast and north regions which have the highest incidences of chonalgiocarcinoma (CCA). *O. viverrini* causes the disease opithorchiasis, and its has been classified as a group 1 biological carcinogen. Humans, dogs, and cats become infected with *O. viverrini* by ingesting raw or undercooked fish containing infective metacercariae. The first human cases of *O. viverrini* infection were reported in Thailand 100 years ago, and it's still a problem at the community level. Based on data for the year 2009, more than 6 million people were infected with *O. viverrini*. Associated medical care and loss of wages in Thailand costs about $120 million annually. This review highlights the current status of *O. viverrini* infection in communities of Thailand through active surveillance for the five years period from 2010 and 2015. A total of 17 community-based surveys were conducted, most in the northeast region. Some 7 surveys demonstrated a high prevalence over 20%, and the highest was 45.7%. Most commonly infection was found in age group of 35 years and older, males, and agricultural workers. Although, the national prevalence may be decreasing but the results show that the *O. viverrini* infection is still high in communities of the northeast region. Therefore, the focus in populations living in northeast Thailand should be screening of infection and changing their eating behavior.**

Keywords: Opisthorchis viverrini - current status - Thailand

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Introduction

Opisthorchis viverrini is a trematode parasite that attacks the area of the bile duct including intra and extra-hepatic bile ducts. *O. viverrini*, Southeast Asian liver fluke, is one of the three most medically important species in the family Opisthorchiidae (King and Sholz 2001; Kaewkes 2003). *O. viverrini* infection is acquired by human, dog, and cats ingest raw or undercooked fish (Sitthithaworn et al., 2003; Kaewpitoon et al., 2007). It causes the disease opithorchiasis and related to a cancer of the gall bladder and/or its ducts; cholangiocarcinoma (CCA) which this CCA is commonly found the high incident in Thailand (Sripa et al., 2007; Kaewpitoon et al., 2008a). In 2009, *O. viverrini* has been classified by the International Agency for Research on Cancer (IARC), World Health Organization (WHO) as a group 1 biological carcinogen in which its capable of causing cancer in human (Sripa et al., 2012). The first human case of *O. viverrini* infection was reported in Thailand (Leiper 1915), to date, it has been reported a serious public health problem in Thailand, Lao People's Democratic Republic, Vietnam, and Cambodia (Yong et a., 2010; Sitthithaworn et al., 2012). Particularly, in the northeast and north region of Thailand, where have been a high incident of *O. viverrini* and CCA (Sripa et al., 2007; Sitthithaworn et al., 2012). Opisthorchiasis has received less attention and it is a neglected disease in Asia, its affect the poor and poorest people (Sripa 2008). In addition, medical care and loss of wages in Thailand costs about $120 million annually (Muller and Wakelin 2002) or $120 million per year can cost Northeast Thailand only (King and Sholz 2001).

Community-based surveys in Thailand have been reported. Update on prevalence and distribution is necessary to summarize, therefore, this review highlights the current status of *O. viverrini* infections in the communities of Thailand. A mini-review was conducted to update the current status of *O. viverrini* in Thailand

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throughout the active surveillance study. The electronic databases PubMed, MEDLINE, Scopus, Web of Science, and Google Scholar were searched with keywords "*Prevalence of Opisthorchis viverrini*", "*Opisthochis viverrini infection*", "*current status of Opisthorchis viverrini*", "*Opisthorchis viverrini in Thailand*". The research articles with five years periods from 2010 and 2015 study in human, were included.

Life Cycle and Transmission

O. viverrini has a freshwater snail as the first intermediate hosts, in which asexual reproduction takes place, and freshwater cyprinid fishes as second intermediate hosts. Humans, dogs and cats, act as definitive hosts, in which sexual reproduction occurs (Young et al., 2010). The first intermediate hosts, freshwater snails (genus Bithynia), ingest the eggs from which the miracidia; asexual, and then a cercaria stage; the free swimming larval stage, is shed from the infected snails. The cercaria penetrates into a cyprinoid fish; the second intermediate host, encysts in the fins, skin and musculature of the fish, and becomes a metacercaria (World Health Organization 1995; Muller and Wakelin 2002; Tohamy and Mohamed 2006; Laha et al., 2007). The second intermediate hosts habitats in the freshwater with stagnant or slow-moving waters mainly ponds, river, aquaculture, swamps, rice fields (Keiser and Utzinger 2007). The metacercariae; the infective stage is ingested by fish-eating mammals; definitive hosts, including human, dogs and cats. Infection is acquired when human ingest raw or undercooked fish. Dishes of raw fish are common in the cuisine of Thailand mainly koi-pla, larb-pla; raw fish in spicy salad, pla-ra, pla som and Som fak; variety of salted semi-fermented fish dishes (World Health Organization 1995; Kaewpitoon et al., 2008). The young adult worm escapes from the metacercarial cyst in the upper small intestine and then migrates through the ampulla of Vater into the biliary tree, where it develops to sexual maturity over four to six weeks, thus completing the life cycle. The lifespan of *Opisthorchis viverrini* is over 10 years (Harinasuta, and Harinasuta 1984).

Current status of *O. viverrini* infection in Thailand during 2010-2015

In Thailand, the first nationwide survey of the four regions of Thailand during 1980-1981 revealed an overall prevalence of *O. viverrini* infection of 14%. The highest of infection was found in the Northeast (34.6%), and flowed by the Central (6.3%), the North (5.6%) and the South (0.01%) regions (Jongsuksuntigul and Imsomboon 2003; Sithithaworn et al., 2012). Since then, the average national prevalence of infection has declined to 8.7% in the year 2009, with the intensive and continuous control programs and public health service activities. This figure indicates that more than 6 million are infected with *O. viverrini* in Thailand, particularly in the north and northeast regions (Sithithaworn et al., 2012). The prevalence of *O. viverrini* infection remains high in various parts of the country, especially in northeast Thailand and particularly in wetland rural areas where a large proportion of the community work in agriculture and continue the traditional practice of eating raw or undercooked cyprinoid fish products. The national control program seems to have had little impact in many of these areas, and it has been difficult to make precise assessments of the overall effectiveness of the program (Sripa et al., 2007; Sitthithaworn et al., 2012).

In this review highlight the current prevalence of *O. viverrini* in the communities of Thailand during five years period 2010-2015, data is shown in Table 1. No survey of *O. viverrini* infection in 2010 in which search through out electronic standard database included Thai-TCI. In year 2011, 2 articles have been reported. A descriptive cross-sectional study was carried out in Khon Kaen province, northeast region. There were 338 sample subjects aged between 20-60 years, from urban, semi-urban and rural areas. Almost one third (32%) reported testing positive for *O. viverrini* eggs in stool (Promthet et al., 2011). The border provinces included Nan in the north, Ubon Ratchathani and Khon Kaen in the northeast, were collected stool samples and examinations. The helminthic infections were examined by using Kato thick-smear technique. Among a population sample of 109 males and 143 females in lowland Nan, with ages ranging between 15-85 years, 74 (29.4%) tested positive for the presence of Opisthorchis-like eggs. The results of the study in highland Nan were very different: Opisthorchis-like eggs were only found in one subject (0.5%) out of the 223 hill-tribe members. In Ubon Ratchathani, population sample of 144 males and 152 females with ages ranging between 15-82 years, 19 (6.4%) tested positive for the presence of *Opisthorchis*-like eggs. In Khon Kaen, population sample of 108 males and 113 females with ages ranging between 15-76 years, 16 (7.2%) tested positive for the presence of *Opisthorchis*-like eggs, respectively.

In 2012, a total of 7 community-based surveys was reported. Of 435 stool samples from Mahasarakham province was prepared by formalin-ether concentration technique and examined. 5.74% of subject was infected with *O. viverrini* (Thanchomnang et al., 2012). Active surveillance on opisthorchiasis was performed in 8,936 males and females aged from 20 to 60 years from 90 villages of Khon Kaen province, northeast Thailand. All were stool-examined for *O. viverrini* infection by standard quantitative formalin/ethyl acetate concentration technique. 3,359 participants (37.59%) with stool *O. viverrini* egg positive, this study emphasizes the current status of high *O. viverrini* infection rate. Of these participants with stool egg positive underwent ultrasonography of the upper abdomen for CCA surveillance (Mairiang et al., 2012). The cross-sectional study in a prospective cohort study was to examine the prevalence and co- infection of intestinal parasites among northeastern Thai rural residents, recruited into the Khon Kaen Cohort Study (KKCS), and who were residing in areas of high-risk for developing CCA. On recruitment, subjects testing using the formalin ethyl-acetate concentration technique. 18,900 of cohort subjects, and 45.7% were found to be positive for *O. viverrini* infection. According to a mapping analysis, a higher CCA burden was correlated with a higher prevalence and a greater intensity of *O. viverrini*

(Songserm et al., 2012). A prospective research project designed to monitor the impact of the national control program in rural communities located in a northeastern province and at high risk of *O. viverrini* infection. 1,569 villagers, aged 20-65 years, living in Yasothon province were examined and found that 38.68% were infected with *O. viverrini*. Males were slightly more likely to be infected than females, and the infection was found to be positively associated with age in both males and females (Saengsawang et al., 2012). In lower northeast was performed, a community-based cross-sectional survey of *O. viverrini* infection was conducted among 333 elderly in 17 districts of Surin province, during one year period from January to December 2011. *O. viverrini* infection was determined using Kato's Thick Smear technique. Overall intestinal parasitic infection was 16.2%, predominantly in *O. viverrini* (9.91%). The *O. viverrini* infection was found higher in males (13.8%) than females (7.83%), and frequently in elderly 60-70 year old with 14.2% (Kaewpitoon et al., 2012). In addition, Kaewpitoon et al., (2012) have been reported the prevalence of *O. viverrini* infection in Nakhon Ratcahsima where is located near Surin province. A cross-sectional survey was conducted during a one year period from October 2010 to September 2011, the infection was determined using a modified Kato's thick smear technique. A total of 1,168 stool samples were obtained from 516 males and 652 females, aged 5-90 years. Stool examination showed that 2.48%

Table 1. Community-based Surveys of *O. viverrini* Infection in Thailand During 2010-2015, by Study Design, Diagnostic Method, Number of Case, Prevalence, and Investigator

Study design	Method	No. of cases	Prevalence	Investigators
Case-control study	Modified Kato-Katz technique	351	33.3	Chudthaisong et al. 2015
Cross-sectional analytic study	Modified Kato-Katz technique	254	15	Chaiputcha et al. 2015
Cohort study	Modified formalin/ethyl acetate concentration technique /indirect ELSIA	469	7	Yeoh et al., 2015
Cross-sectional study	Modified Kato Katz method	3,916	22.7	Thaewnongiew et al., 2014
Cross-sectional study	Formalin-ethyl acetate concentration methods	253	26.9	Boonjaraspinyo et al., 2013
Cross-sectional study	Kato thick smear technique	684	37.2	Saengsawang et al., 2013
Community-based prospective Cohort study	Kato and formalin-ethyl acetate concentration technique	1,204	18.6	Suwannahitatorn et al., 2013
Cross-sectional survey	Formalin-ether concentration technique	331	13.9	Yahom et al., 2013
Cross-sectional survey	Modified Kato's thick smear technique	1,168	2.48	Kaewpitoon et al., 2012
Community-based cross-sectional survey	Kato's Thick Smear technique	333	9.91	Kaewpitoon et al., 2012
Cross-sectional study	Kato's Thick Smear technique	1,569	38.7	Saengsawang et al., 2012
Cross-sectional study	Formalin-ether sedimentation and high annealing temperature random amplified polymorphic DNA PCR methods	316	6.54	Wongsawad et al., 2012
Cross-sectional study in a prospective cohort study	Formalin ethyl acetate concentration technique	18,900	45.7	Songserm et al., 2012
Cross sectional study	Formalin/ethyl acetate concentration technique	8,936	41.5	Mairiang et al., 2012
Cross sectional study	Formalin-ether concentration technique	435	5.74	Thanchomnang et al., 2012
Descriptive cross-sectional study	Kato's Thick Smear technique	338	32	Promthet et al., 2011
Cross sectional study	Kato-Katz technique	Nan (475)* Khon Kane (221) Ubon Ratchathani (296)	15.79 7.2 6.4	Anantaphruti et al., 2011

*Number of case in that province

Table 2. Community-based Surveys of O. viverrini Infection in Thailand during 2010-2015, by Age, Gender, Occupation, and Location of Survey, Investigator

Study survey (province)	Age	Gender	Occupation	Investigators
Nong Khai	35-54, >54	Male	Agriculture	Chudthaisong et al. 2015
Mahasarakham	30-44 45-59 >59	Male	Agriculture	Chaiputcha et al. 2015
Khon Kaen	35-44	-	-	Yeoh et al., 2015
Nakhonphanom Sakonnakhon Nongkhai	40-49	Male		Thaewnongiew et al., 2014
Khon Kaen	>60	Male		Boonjaraspinyo et al., 2013
Yasothon	20-35	Male	Government service	Saengsawang et al., 2013
Chachengsao	25-59 >59	Male	Agriculture	Suwannahitatorn et al., 2013
MahasarakhamKalasin	>45	Male	Agriculture	Yahom et al., 2013
Nakhon Ratchasima	51-60	Male	Agriculture	Kaewpitoon et al., 2012
Surin	60-70	Male	Agriculture	Kaewpitoon et al., 2012
Yasothon	36-55 56-65	Male	Agriculture	Saengsawang et al., 2012
Chiang Mai	-	-	-	Wongsawad et al., 2012
Khon Kaen Cohort Study (KKCS)	-	Male	-	Songserm et al., 2012
Khon Kaen	40-49	Male	Agriculture	Mairiang et al., 2012
Mahasarakham	-	Male	-	Thanchomnang et al., 2012
Khon Kaen	-	-	-	Promthet et al., 2011
Nan, Khon Kaen, Ubonratchathani	-	-	-	Anantaphruti et al., 2011

were infected with *O. viverrini*. Males were slightly more likely to be infected than females, but the different was not statistically significant. Positive results were evident in 16 of 32 districts, the highest prevalence being found in Non Daeng with 16.7%, followed by Pra Thai with 11.1%, Kaeng Sanam Nang with 8.33%, and Lam Ta Men Chai (8.33%) districts. A high throughput method was employed to identify mixed infection between *O. viverrini* and minute intestinal fluke in the north region. 316 fecal specimens of people living along the Mae Ping River, Chomtong district, Chiangmai province, were examined seasonally for trematode eggs using a compound microscope. Positive cases were analyzed in HAT-RAPD, DNA profiles were compared with adult stages to determine the actual species infected, and specific DNA markers of each fluke were also screened. The results showed that 6.54% of *O. viverrini* was found only in the hot-dry season. This study demonstrates the mixed infection of *O. viverrini* and Haplorchis taichui and confirms the extended distribution of *O. viverrini* in northern Thailand (Wongsawad et al., 2012).

In 2013, *O. viverrini* infection was examined in 331 stool samples from Maha Sarakham and Kalasin province where located in the upper northeast region, by formalin-ether concentration technique. *O. viverrini* infection (13.90%) was the most common pathogenic intestinal parasitic infection, followed by Strongyloides stercoralis (11.47%) and Taenia sp (1.81%) (Yahom et al., 2013). A prospective research project to monitor the impacts of a national liver fluke control program in a rural community of northeast Thailand, a sample of 684 villagers aged 20-65 years was tested for infection using the Kato thick smear technique. The overall prevalence of *O. viverrini* infection was 37.2% and was highest in the 20-35 year age group. As many as 91.8% reported eating fish dishes known to place them at risk of infection (Saengsawang et al., 2013). The village scale in Khon Kaen province, northeastern Thailand was surveyed from March to August 2013. A total of 253 stool samples from 102 males and 140 females, aged 2-80 years, were prepared using formalin-ethyl acetate concentration methods. The most common parasite found was *O. viverrini* (26.9%), followed by S. stercoralis (9.5%), Taenia spp. (1.6%), Echinostomes (0.4%), and hookworms (0.4%) (Boonjaraspinyo et al., 2013). While, one study in central region was conducted. A prospective cohort study was conducted to evaluate the incidence of *O. viverrini* infection in Chachengsao province by using Kato and formalin-ethyl acetate concentration technique. The results indicate that the prevalent and incident of *O. viverrini* infection were 18.6% and 21.4%, respectively. Consumption of chopped raw fish salad, Koi pla and age 60 years and older were independently associated with *O. viverrini* infection (Suwannahitatorn et al., 2013).

In 2014, an investigation of prevalence and risk factors for opisthorchiasis in 3,916 Thai residents of Nakhon Phanom, Sakon Nakhon, and NongKhai province who were 15 or over, and stool examinations for parasite eggs (using the Modified Kato Katz method) was reported. The prevalence of opisthorchiasis was 22.7%. The province with the highest prevalence was Nakhorn Phanom (40.9%;

female to male ratio =1:1.2). The age group with the highest prevalence was 40-49 year olds. All age groups had a prevalence >20% (Thaewnongiew et al., 2014). In 2015, the prevalence of *O. viverrini* infection in the cohort subjects (as well as new subjects) was investigated using faecal egg counts. *O. viverrini* infection rates in the same individuals of the cohort were lower in 2006 than in 1992, was 7.0%. Also, by studying the period effect, the current 35-44 year olds had a 12.4% (95% CI 3.9% to 20.9%) lower prevalence of *O. viverrini* infection than the 35-44 year olds in 1992 (24.2% versus 11.8%) (Yeoh et al., 2015). The cross-sectional analytic study was to investigate the prevalence for *O. viverrini* infection in 254 household representative aged 15 years or older living in the most urbanized part of Chiang Yuen municipality in Mahasarakham province, northeastern Thailand. All participants provided stool samples in which were examined using the modified Kato-Katz procedure. The overall prevalence of *O. viverrini* infection was 15.0%, and in the multivariate analysis male gender was found to be significantly and positively associated with *O. viverrini* infection (ORadj=9.75, 95%CI: 34.03-23.58) while education to secondary school level or above was a significant protective factor (ORadj=0.30, 95%CI: 0.12-0.74) (Chaiputcha et al. 2015). Among 516 people in Nong Khai province in July 2013 was examined *O. viverrini* infection. Stool specimens were examined for intestinal parasites within hours after collection using a normal saline wet preparation and the modified Kato- Katz technique. Of 117 (22.67%) participants have a positive test result for *O. viverrini* infection (Chudthaisong et al., 2015)

The *O. viverrini* infection was found in age between 20-80 year old, and the most frequently in 35-55 year old. Moreover, older people are still found high infection, particularly in age over 60 year old. Infection in gender was characterized and found that male was slightly found more than female. In addition, occupation with agriculture was the most frequently *O. viverrini* infection. Characteristic data are shown in Table 2.

Conclusions

The results show that the prevalence of *O. viverrini* infections in Thailand is still high, particularly in the northeast region. Proactive education about dietary habits, personal hygiene, and sanitation should be provided to the people in the rural community to reduce the prevalence of *O. viverrini* infections. In order to reduce the prevalence of opisthorchiasis, the focus in populations living in Northeast Thailand should be changing their eating behaviors as appropriate to their tradition and context.

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