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Short communication

Changing patterns of prevalence in *Opisthorchis viverrini* sensu lato infection in children and adolescents in northeast Thailand

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ABSTRACT

Infection with the liver fluke *Opisthorchis viverrini* sensu lato (s.l.), a group 1 carcinogen, is the most important risk factor for developing cholangiocarcinoma (CCA) in Southeast Asia. Cholangiocarcinoma is a fatal disease with the world's highest incidence being found in northeast Thailand. Liver fluke infection occurs through eating raw or partially cooked cyprinid fish containing metacercariae and, therefore, the control of *O. viverrini* s.l. infection should lead to a reduction in CCA incidence. In this report, we review and analyze the age-prevalence profile data of *O. viverrini* to reveal temporal changes in patterns of prevalence pre- and post-control programs in Thailand. The profiles of *O. viverrini* prevalence have transformed from high prevalence in school children prior to 1983 to low prevalences after 1994. This pattern strongly suggests the influence of the health education program on the likelihood of school children becoming infected. In conjunction with current developments in health and socioeconomic conditions, we predict that the incidence of CCA will be reduced with time as the population cohorts that experienced the education programs reach the age at which CCA is most likely to develop, i.e. >50 years. The lessons learned in Thailand may be applicable to other areas endemic for human liver flukes.

The incidence of CCA in northeast Thailand is the highest in the world (Shin et al., 2010). In Khon Kaen province, it ranged from 93.8 to 317.6 per 100,000 persons/year from 1990 to 2001 (Sriamporn et al., 2004). Data presented by the National Cancer Registry of Thailand also shows that liver and bile duct cancer are the most common cancers in both males and females at the age of >40 years in northeast Thailand, unlike the rest of the country (Khuhaprema et al., 2013). CCA is a particularly problematic disease as it is most commonly diagnosed at a late stage at which cure is not possible and palliative care is the only option (Kamsa-ard et al., 2011; Khuntikeo et al., 2016). CCA in the northeast of Thailand is strongly associated with infection by the liver fluke *Opisthorchis viverrini* sensu lato (s.l.) species complex (Saijuntha et al., 2007), which is classed as a group 1 carcinogen (Sripa et al., 2007, 2012; IARC, 2012; Sithithaworn et al., 2014). Infection occurs through eating raw, marinated or partially cooked cyprinid fish containing infectious metacercariae (Petney et al., 2013), a very common traditional behaviour in this part of Thailand (Grundy-Warr et al., 2012), and may lead to CCA decades after infection (Sithithaworn et al., 2014). This indicates that effective control of *O. viverrini* s.l. infection, and of its associated CCA, could be affected via education to prevent or reduce eating raw, (cyprinid) fish. The control of *O. viverrini* s.l. infection should lead to a reduction in CCA incidence.

Measures aimed at the control of *O. viverrini* s.l. have been in place since 1950 when a program to control helminths was initiated in four north-eastern and one southern Thai province. These programs can be divided into three phases: Phase 1: sporadic and

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Table 1
Prevalence of infection with *Opisthorchis viverrini* in humans by age group.

Year	Date	Locality	n	Reference	Age-related prevalence (%)								
					0–4	5–9	10–14	15–19	20–29	30–39	40–49	50–59	≥60
1955	1951–1952	5 northeastern provinces	6334	Sadun (1955)	21.70	36.40	51.00	65.60	65.60	62.40	62.40	62.40	62.40
1980	March-June 1980	Chonnabot, Khon Kaen	1651	Upatham et al. (1984)	32.10	39.80	95.60	96.60	96.50	96.90	96.90	96.90	96.90
1980	March-June 1980	Chonnabot, Khon Kaen	1645	Brockelman et al. (1987)	32.26	90.37	95.63	96.08	96.43	96.34	96.95	96.92	96.15
1981	March-June 1981	Chonnabot, Khon Kaen	1585	Brockelman et al. (1987)	41.60	92.42	98.41	97.85	95.61	96.92	98.77	98.50	96.88
1982	March-June 1982	Chonnabot, Khon Kaen	1447	Brockelman et al. (1987)	29.27	80.90	93.85	93.86	94.51	93.96	96.13	93.43	90.32
1981–1983	During a 30 month period between May 1981 and 31 October 1983	Rural area in northeast	433	Kurathong et al. (1987)	11.76	50.00	80.0	80.00	76.70	88.30	86.10	86.50	82.90
1981–1982	1981 and 1982	Villages far from river in Nong Khai and Loei	761	Tesana et al. (1991)	20.80	53.85	53.64	53.64	66.02	61.54	64.04	52.27	53.49
1994	July to October 1994	19 northeastern provinces	1912	Jongsuksuntigul and Imsomboon (1997)	4.60	9.19	8.32	5.86	15.38	18.95	15.38	10.51	10.09
2003	During May 2003	Khukan District, Si Sa Ket	774	Nithikethkul et al. (2004)	4.50	4.50	2.70	2.70	14.50	12.40	9.40	14.80	14.50
2010–2011	October 2010 to September 2011	Nakhon Ratchasima	1168	Kaewpitoon et al. (2012)	–	0	0	2.13	1.96	2.58	2.66	2.75	2.72
2013	March to August 2013	Shi and Pong Rivers flow in Khon Kaen Province	253	Boonjaraspinyo et al., (2013)	Prevalence age under 20 = 0				27.30	27.30	24.00	24.00	32.90
2013–2014	September 2013 to July 2014	Surin	510	Kaewpitoon et al., (2015)	–	0	0	0	1.79	0	1.72	4.62	15.14

local health education (from 1950 until the early 1980s), Phase 2: health education and the use of the anthelminthic drug praziquantel (from the early 1980s until 2000), Phase 3: reduced funding due to economic recession, as well as a diversion of resources to other health priorities (Sripa et al., 2015) more topical emerging diseases such as avian influenza. During Phase 2, the liver fluke control program was integrated into the 6th five-year National Public Health Development Plan during which all health facilities in northeast Thailand assisted in the diagnosis and treatment of infection (Jongsuksuntigul and Imsomboon, 2003). Currently, because of the recognition of the high mortality caused by CCA in Thailand (Khuntikeo et al., 2016), the government recently ratified a ten year program to eliminate *O. viverrini* infection.

As CCA development can occur decades after the initial infection with *O. viverrini* s.l., education at the level of school children is particularly important (World Health Organization, 2011; Ziegler et al., 2011). A preliminary study indicates that recent school health education programs are providing increased background knowledge of *O. viverrini* s.l. and CCA, however this stills requires confirmation (Laithavewat et al. unpublished data). Control of opisthorchiasis and, subsequently, CCA in Thailand via education has been multifaceted, including education at school, village and regional levels, a mobile team for stool examination to diagnose individuals with *O. viverrini* infection, as well as treatment programs using praziquantel (Jongsuksuntigul and Imsomboon, 1998). In the northeast of Thailand, the overall prevalence of *O. viverrini* s.l. infection dropped from 34.6% in 1981 to a low of 12.4% in 1996 with a small increase to 15.7% in 2001 (Jongsuksuntigul and Imsomboon, 2003). Nevertheless, local prevalences may be high in the adult population (35–80%) (Saengsawang et al., 2013; Thaewnongiew et al., 2014).

Once the medical significance of *O. viverrini* s.l. infection was recognized, a series of epidemiological studies were carried out to determine the prevalence of the disease in the Thai population. The first major study was a cooperative undertaking between the Thai Ministry of Public Health and the United States Special Technical and Economic Mission to Thailand (Sadun, 1955). This study found that the prevalence of infection in the northeast of Thailand increased continuously from the 0–4 age group (21.7%) through the 5–9 group (36.4%), the 10–14 year olds (51%) before plateauing at about 63% for individuals 15 years or older (Sadun, 1955). High prevalences in school children continued to be found by Upatham et al. (1984) Upatham et al. (1984; 0–4 years 32%, 5–9 years 39.8%, 10–14 years 95.6% and 15–19 years 96.6%), Brockelman et al. (1987; >50% from the age of 4 years and >90% for 8–19 year olds), Kurathong et al. (1987; 50–80% for 5–19 year old children from rural populations) and Tesana et al. (1991; 0–4 years 20.80%, 5–9 years 53.85%, 10–19 years 53.64%, 20–29 years 66.02%, 30–39 years and >40 years >50%) (Table 1). Moreover, after treatment with praziquantel the rate of reinfection was high (80% for the 0–9 age group and 84% for the 10–19 age group one year after treatment, (Upatham et al., 1988). Children infected at the this time of high prevalence are among those adults now approaching or exceeding the age of 40 who show a high risk of developing CCA (Kamsa-ard et al., 2011; Khuntikeo et al., 2015). In order to predict the progression of the incidence of CCA in the northeast Thai population it is therefore necessary to determine how the opisthorchiasis prevalence rates in school children developed after the implementation of control measures.

The implementation of widespread control measures coincided with a very substantial reduction in prevalences of *O. viverrini* s.l. in the northeast: 6–8% for 10–19 year olds (Jongsuksuntigul and Imsomboon, 1997), 5.7% for 8–12 year olds (Khampitak et al., 1997), 4.5% for <10 year olds and 2.7% for 10–20 year olds (Nithikethkul et al., 2004); 5.6% for 6–12 year-olds (Khampitak et al., 2006); and 0% (Boonjaraspinyo et al., 2013; but with a sample size of only 6) (Fig. 1). The extreme reductions in prevalence strongly suggest