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Original Contribution

Untangling the Complexity of Liver Fluke Infection and Cholangiocarcinoma in NE Thailand Through Transdisciplinary Learning

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Abstract: This study demonstrates how a transdisciplinary learning approach provided new insights for explaining persistent *Opisthorchis viverrini* infection in northern Thailand, as well as elucidating problems of focusing solely on the parasite as a means of addressing high prevalence of cholangiocarcinoma. Researchers from diverse backgrounds collaborated to design an investigative homestay program for 72 Singaporean and Thai university students in five northeast Thai villages. The students explored how liver fluke infection and potential cholangiocarcinoma development are influenced by local landscape dynamics, aquatic ecology, livelihoods, food culture and health education. Qualitative fieldwork was guided daily by the researchers in a collaborative, co-learning process that led to viewing this health issue as a complex system, influenced by interlinked multidimensional factors. Our transdisciplinary experience has led us to believe that an incomplete understanding of these linkages may reduce the efficacy of interventions. Further, viewing liver fluke infection and cholangiocarcinoma as the same issue is inadvisable. Although *O. viverrini* infection is an established risk factor for the development of cholangiocarcinoma, multiple factors are known to influence the likelihood of acquiring either. Understanding the importance of the current livelihood transition, landscape modification and the resulting mismatch between local cultures and new socio-ecological settings on cholangiocarcinoma initiation and liver fluke transmission is of critical importance as it may help readjust our view of the respective role of *O. viverrini* and other socioeconomic risk factors in cholangiocarcinoma etiology and refine intervention strategies. As demonstrated in this study, transdisciplinary approaches have the potential to yield more nuanced perspectives to complex diseases than research that focuses on specific aspects of their epidemiology. They may therefore be valuable when designing effective solutions to context-sensitive diseases such as liver fluke infection and cholangiocarcinoma.

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The *O. viverrini*-Cholangiocarcinoma Conundrum

The *Opisthorchis viverrini* sensu lato (hereafter simply referred to as *O. viverrini*) species complex, also known as the Southeast Asian liver fluke, is endemic in Thailand, Lao PDR, Cambodia and southern Vietnam (Andrews et al. 2008; Kaewpitoon et al. 2008; Sithithaworn et al. 2014). Liver fluke infection is particularly prevalent in northeastern Thailand (also known as the Isaan Region) and Lao PDR, where up to 70–90% of the inhabitants in some rural communities are infected (Sripa et al. 2007; Sithithaworn et al. 2012a). This is often attributed to the regionally widespread cultural habit of consuming and sharing traditional preparations of raw or partially cooked fish (Grundy-Warr et al. 2012). In this region, dishes and condiments such as *plaa som* (fermented fish) and *plaa raa* (fermented fish sauce), which are not cooked sufficiently to kill *O. viverrini* metacercariae, are shared and consumed almost daily (Prasongwatana et al. 2013).

As with other helminths, *O. viverrini* is thought to have evolved mechanisms that modulate host immune responses toward an anti-inflammatory/regulatory phenotype (Magen et al. 2013; Robinson et al. 2013) to insure long-lasting infestation. As a consequence, the vast majority of infections are asymptomatic, and not all chronically infected individuals develop advanced hepatobiliary conditions (Sripa et al. 2012). In some cases, however, especially when worm burden is high and down-regulatory processes are dysfunctional, *O. viverrini* infection can result in the clinical disease opisthorchiasis and induce serious hepatobiliary pathology such as fibrosis, hepatomegaly, cholangitis and gallstone formation (Mairiang et al. 2012). *O. viverrini* infection has been reported to be a risk factor inducing cholangiocarcinoma, an aggressive, asymptomatic biliary duct cancer with a very poor prognosis (Smout et al. 2011; Sripa et al. 2012; Sithithaworn et al. 2014).

As depicted in Figure 1, *O. viverrini* is a complex-life-cycle trematode that has numerous distinct life stages (i.e., egg, miracidium, sporocysts, redia, cercariae, metacercariae and adult worms). The parasite requires freshwater snails of the genus *Bithynia* and cyprinid fish as first and second intermediate hosts. It is acquired by humans—the dominant final host (Petney et al. 2013)—through the consumption of raw or partially cooked fish containing the infective stage of the parasite, the metacercariae. Human infection develops when metacercariae excyst in the duodenum and migrate to the smaller, proximal bile ducts under the surface of the liver, where they mature (Figure 1). Eggs of the adult parasite are passed out in the stool. When egg-bearing human waste enters freshwater habitats of the intermediate hosts, the transmission cycle is nearly complete. Collectively, the above processes create a multifaceted epidemiological setting, concurrently implicating local ecological, hydrological, cultural and livelihood aspects. Transmission likelihood is determined by mutual interaction of these diverse socio-ecological influences. Disease indicators, such as infection prevalence, infection intensity, parasite reproduction and survival, therefore cannot be understood as purely ecological or biological phenomena.

The association between chronic *O. viverrini* infection and cholangiocarcinoma is perhaps the strongest reported connection between a parasite and a cancer (Sripa et al. 2015). Nonetheless, the mechanisms by which *O. viverrini* infection contributes to this high cancer prevalence remain unclear (*ibid.*). Further complicating this causal relationship is the presence of various other widely accepted risk factors that contribute to cholangiocarcinoma development. These include genetics, diet and lifestyle—particularly alcoholism and fermented fish consumption, both of which are extremely common in the region (Shaib and El-Serag 2004; Honjo et al. 2005; Khan et al. 2008; Songserm et al. 2012). To date, there remains a lack of comprehensive explanations for the region's persistently high prevalence of *O. viverrini* infection and cholangiocarcinoma (Sripa et al. 2015).

Given the multiple dimensions of the *O. viverrini*-cholangiocarcinoma health conundrum, it is crucial to frame the issue in a way that appreciates these complex linkages. Thus far, progress has been hindered by a lack of clear strategy for filling research gaps. To overcome inertia in public health paradigms and improve interventions, transdisciplinary studies may be an ideal way forward. These approaches have the potential to contribute significantly to disease prevention responses, particular by helping fill the gaps in understanding the social ecology and

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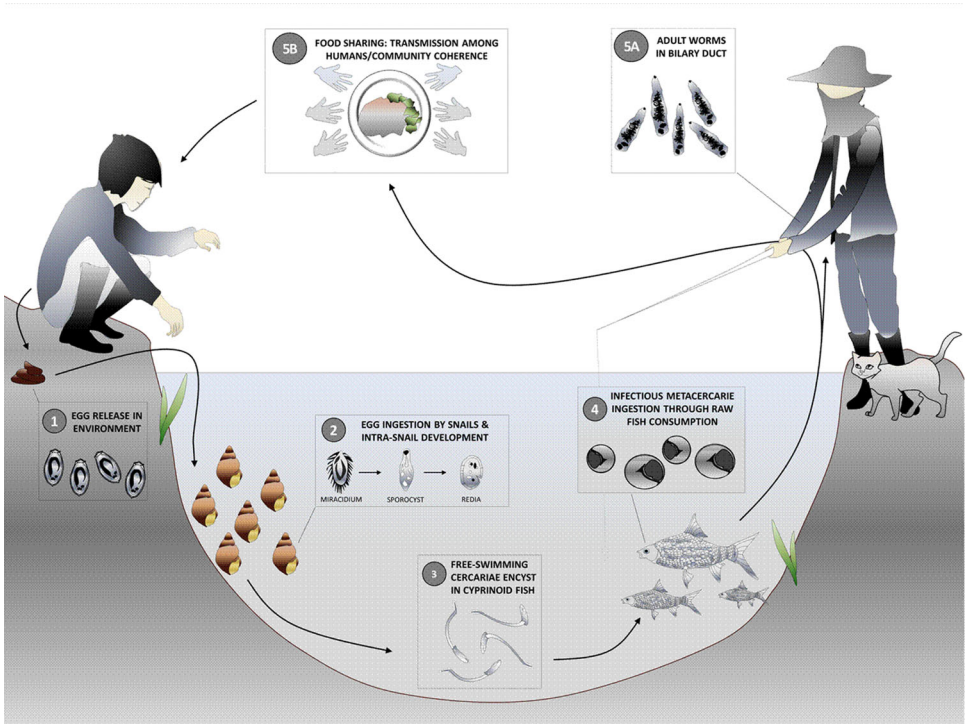

Figure 1. Life cycle of *O. viverrini* is complex because it involves human and animal intermediate hosts across various life stages. Human infection occurs when infected fish are consumed raw or partially cooked (including smoked, pickled and salted). Metacercariae in the fish escapes from the cyst in the small intestine and enter the bile ducts, where they mature sexually. Eggs of the adult worms are carried in bile fluid and passed out in feces. Egg-bearing human waste may enter the freshwater habitats of *Bithynia* snails, which ingest the eggs. Within the snails, miracidium hatch and develop into sporocysts that undergo asexual multiplication and develop into rediae and cercariae. These free-swimming cercariae emerged from the snail and actively search for a fish host, most often from the cyprinidae family. They penetrate the tissues and skin and develop into cystic metacercariae, the stage infective to humans and other fish-eating mammals (Sithithaworn et al. 2014; Sripa et al. 2011) (Color figure online).

ecological research on liver flukes (WHO 2012). In *O. viverrini* and cholangiocarcinoma research, transdisciplinary approaches might therefore not only offer fresh conclusions, but also represent shifts into a new era of collaborative studies and healthcare.

An opportunity to attempt such an approach presented itself in tandem with an international university exchange program, involving Khon Kaen University's Faculty of Medicine, the KKU Faculty of Humanities and Social Sciences and the National University of Singapore's Department of Geography. Researchers and lecturers collaborated to organize a village homestay-cum-research study, with the dual objective of training students in field research and gleaning interdisciplinary insights into the *O. viverrini*-cholangiocarcinoma issue. Here we describe this transdisciplinary co-learning experience, highlighting the multifaceted experience of explaining how its results contribute to broader and current efforts to rethink this regionally persistent medical problem. We present the ways in which this collaborative exercise contributed to our revised perspectives of the *O. viverrini*-cholangiocarcinoma issue.

A Transdisciplinary Approach

A transdisciplinary approach involves "multiple scientific disciplines (interdisciplinarity) focusing on shared problems and the active input of practitioners from outside academia" (Brandt et al. 2013, p. 1). Transdisciplinary teaching and learning recognizes that in-depth understanding often transcends subject area boundaries and that engaging in this type of learning provides practice-based learning to participants (Merck and Beermann 2015). Accordingly, our research team involved not just academic faculty, but also representatives from the Thai Ministry of Public Health. Collectively, this brought together expertise from diverse research backgrounds: parasitology, pathology, epidemiology, surgery, ecology,

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hydrology, community healthcare, history, ethnography and geopolitics.

The investigation began with a 1-day summit, where ten researchers working on *O. viverrini* and cholangiocarcinoma issues delivered state-of-knowledge presentations to 72 university students from Singapore and Thailand, who would later be directly involved in fieldwork. Topics ranged from the parasite's life cycle, to the history, epidemiology and prevalence trends of opisthorchiasis and cholangiocarcinoma. Following the summit, five of the speakers, a postdoctoral researcher and two postgraduate students identified major contemporary issues potentially influencing *O. viverrini* transmission and prevalence in a focus group session. These steps were vital for establishing a common understanding of the issue's complex nature and for coherently framing research objectives—typical challenges in transdisciplinary studies (Brandt et al. 2013).

During the focus group session, 23 *O. viverrini*-related issues were identified that could viably be investigated by the students through rural homestays. These issues were then synthesized into five central themes: (1) landscape dynamics, (2) aquatic ecology, (3) food culture, (4) livelihoods and (5) health education. Thereafter, the students were grouped into a "buddy" system with a ratio of 2:1 Singapore to Thai members and placed into homestays at five villages in the adjacent provinces of Khon Kaen and Mahasarakham. At every village, the student groups conducted fieldwork on each of the five themes, using a combination of environmental sampling and ethnographic methods (e.g., interviews, focus groups, participant observation). Thus, at the end of the 1-week homestay period, we had completed a cross-sectional study of how each theme related to *O. viverrini* prevalence and awareness in each village.

By design, Thai and Singaporean students alike were given very few readings on the issue—in the spirit of grounded research, see Glaser (1992) and Dunne (2011). In following, the students were also given only a brief orientation upon arrival at the villages. Surprisingly, virtually all the Thai students were unfamiliar with the liver fluke issue, despite many being from the region. The knowledge base of students was therefore largely framed by the overview presentations at the state-of-knowledge summit on the first day, which had presented only the most broadly accepted science on the *O. viverrini* life cycle and pathogenesis. A balance was sought such that strong views by any one researcher did not carry excessively more weight than those of the collective group. As such, the presentations were given at a level that a novice audience could understand. This approach was adopted because we wanted the students to develop new theories and ideas, rather than test preconceived notions or be biased by stereotypes. Armed with little more than a basic understanding of the liver fluke issue, student groups retained "outsider status," potentially making them "neutral information brokers" (Elliott 1988), compared with those who were familiar with the issue from prior study.

During the research period, the seven researchers and practitioners responsible for designing the study rotated among student groups to monitor progress. A key challenge was refining data collection methods when and where necessary to ensure that fieldwork remained relevant, while keeping the data-gathering process free from "insider" biases as far as possible. Over the years, many of the senior researchers had observed particular assumptions pervading research agendas and healthcare industry in general. An example is the tendency to attribute cholangiocarcinoma persistence solely to an insuperable food culture problem. Further, many authorities within the healthcare sector believe that villagers fully understand the issue, but they simply cannot, or will not, stop eating high risk foods regularly. Such perspectives, coupled with the environmental prevalence of *O. viverrini* and the asymptomatic nature of cholangiocarcinoma, contribute to a widespread sentiment that fighting the cancer is a Sisyphean task. As not all team members agreed on the validity of these beliefs, they were not discussed with the students prior to assigning research projects. Although students were allocated research themes, caution was exercised to avoid steering them one way or the other in support of any one particular "pet" theory. The transdisciplinary design of this study, therefore, created a dynamic, ever-evolving research process that demanded flexibility, self-reflection, pedagogical sensitivity and cooperation.

Adhering to transdisciplinary research approaches forced team members to cross boundaries of expertise every day to push each group project forward (Echaubard et al. 2015). Experienced researchers were challenged to triangulate prior knowledge with new student observations, while concurrently pushing them to formulate new lines of enquiry to better understand site-specific conditions. The result was an intense, dynamic mutual learning process between student observers and researchers, both of whom were frequently operating outside their normal comfort zones. It was crucial to articulate ideas without jargon, to communicate in ways that were understandable to all

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parties, regardless of background and level of expertise. This collaborative, versatile approach led to new perspectives for academics and students alike, enabling a clearer vision of the most crucial linkages between infection and behavior. Critically, this also provided us insights into current and future healthcare possibilities in liver fluke interventions.

Geographical Setting

The Isaan region was selected for our study for various societal and environmental reasons. The annual monsoon gives rise to distinct wet and dry seasons (wet: mid-May to October; dry: mid-October to February), which drastically alter transmission dynamics. Between the wettest months of August and September, cyprinid fish migrations from the upper Mekong increase and localized flooding expands the habitat area of *Bithynia* snails (Brockelman et al. 1986). Livelihoods in this region are also seasonally dependent. Most northeast Thai villagers alternate between wet-season fishing and single- or dual-harvest wet-rice cultivation during the dry season. Wet-rice cultivation accounts for 75% of agricultural land (Haefele et al. 2006), and agriculture is the primary income source for 80% of all northeast Thais (e.g., rice, sugar cane, cassava) (Mekong Institute, 2013). Consequently, many are dependent on water bodies that are both natural (wetlands, lakes, streams) and man-made (rice paddies, irrigation ponds and canals). This connection not only binds the daily life of villagers to environments favorable for the parasite (Petney et al. 2012), but also strongly influences their everyday food culture (Grundy-Warr et al. 2012). In combination, these socio-ecological factors create a setting prime for widespread *O. viverrini* infection.

Khon Kaen University is at the center of cholangiocarcinoma medical research and *O. viverrini*-related control initiatives in northeast Thailand. Thus, simply for the sake of accessibility, villages nearby and in neighboring provinces have been the target of past and ongoing research initiatives. Khon Kaen province also demonstrates a very high prevalence of liver cancer (mainly cholangiocarcinoma) (Khuhaprema and Srivatanakul 2007; Attasara and Sriplung 2012; Sithithaworn et al. 2014). Given that one component of this study involved evaluating health education efforts, it was intuitive to select an area that has received the greatest exposure to various forms and intensity of education. Besides seeking villages across a range of exposure to *O. viverrini* education and control efforts, we also sought those at different stages of urbanization, with varying importance of agriculture, fishing, wet-rice cultivation and migratory occupations. This enabled us to study how the relevance of shared *O. viverrini* drivers may change with time, as villages progress along trajectories of rural-to-urban development. At a broader level, we also sought insights into how ongoing human modifications to the landscape could alter human risk to ecologically driven parasitic diseases in this region. The availability of such villages in close proximity made Khon Kaen province an ideal "base camp" from which to coordinate our learning-based, comparative study across a range of accessible villages.

Visualizing Complexity

Following the homestays, the students presented key results in an open forum and in essays. The common thread running through their findings was the extent to which *O. viverrini* and cholangiocarcinoma pathologies are intimately connected within a system that involves ecology, culture, livelihood changes, education and public health policies. As seen in Figure 2, their influence manifests in infrastructure, local practices and the landscape. These cross-scale linkages introduce non-medical causal trends into the relationship between *O. viverrini* and cholangiocarcinoma, rendering it multi-factorial and nonlinear. Arguably, this complexity had yet to be articulated at the time the research was conducted. A key challenge we faced was how to visualize complex relationships. Inspired by systems dynamics approaches (Meadows 2008), the causal loop diagram in Figure 3 attempts to represent most major linkages between the various drivers of *O. viverrini* transmission and infection patterns observed. As only student findings are depicted, not included are the roles of genetics, evolution, complex ecological interactions and other risk factors less well-known to village communities. Additionally, some relationships have been simplified. Nonetheless, the diagram includes most of the important social and environmental phenomena that were observed and their co-influences.

During the study, it became clear that the main motivation for controlling *O. viverrini* infection in the region was to address the greater concern of high cholangiocarcinoma prevalence (Figure 3). Again, the underlying assumption has been that the parasite is the most important risk factor for the cholangiocarcinoma. In this regard,

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Figure 2. *O. viverrini*–cholangiocarcinoma relationship is complicated by ecology, culture, livelihood changes, education, and public health policies. Clockwise from *top left*: **a** Northeast Thailand's extensive irrigation network employs large pumps to circumvent physical barriers such as roads, enabling transmission of *O. viverrini* eggs to host habitats living far away from wetland areas. Some rice farmers divert excess irrigation water from their fields back to the Lawa Lake (pictured here), which if contaminated with fecal matter, might close the transmission cycle (Fig. 1). **b** Cyprinid fish, the second intermediate hosts of *O. viverrini*, comprise the bulk of fishermen's catch in this region. **c** Health education for schoolchildren effectively uses colorful mind maps and artwork to communicate the dangers of *O. viverrini*. However, efforts to educate adults are sporadic and incomplete, potentially explaining persistent re-infection among older age groups. **d** Improper waste disposal and treatment, such as this standing wastewater pond, increases likelihood of *O. viverrini* egg transmission to other water bodies. In this village, those who live on the edges allow their waste to flow directly into fields behind their homes. **e** Even in villages where livelihoods are transitioning away from fishing and farming, consumption of raw and fermented fish is fueled by dispersed economies that bring freshly-caught and fermented fish to local markets. For fishmongers at the Nong Waeng market in Roi Et, most of their fish catch comes from the Kaeng Loeng Chan Reservoir and the Chi River. It is most commonly sold in the form of *plaa som*, a fermented sour fish dish. **f** At the center of persistent *O. viverrini* risk in northeast Thailand is, inevitably, food culture. The much-loved *som tam* (spicy papaya salad), which contains fermented *plaa raa* fish sauce, is commonly seen at mealtimes along with *khao niao* (sticky rice) and other fermented fish dishes. Photo credits: Chen Meiyi, Charlene Teo, Felicia Kiew, Loh Kai Quan (Color figure online).

intervention follows two essentially different strategies. For individuals without previous infection with *O. viverrini*, safety education (particularly among children) is promoted to increase villager understanding of the complex *O. viverrini*-cholangiocarcinoma issue—but also to discourage consumption of cyprinid fish in unsafe forms—often through "scare tactics" and/or shaming individuals who do so, with the aim of preventing infection. Those individuals who are currently infected or have a history of infection (i.e., those having an increased likelihood of developing cholangiocarcinoma) should, in addition to education and pharmaceutical treatment, be screened to detect early stage cholangiocarcinoma, which is only curable by surgery (Khuntikeo et al. 2015). We found that community edu-

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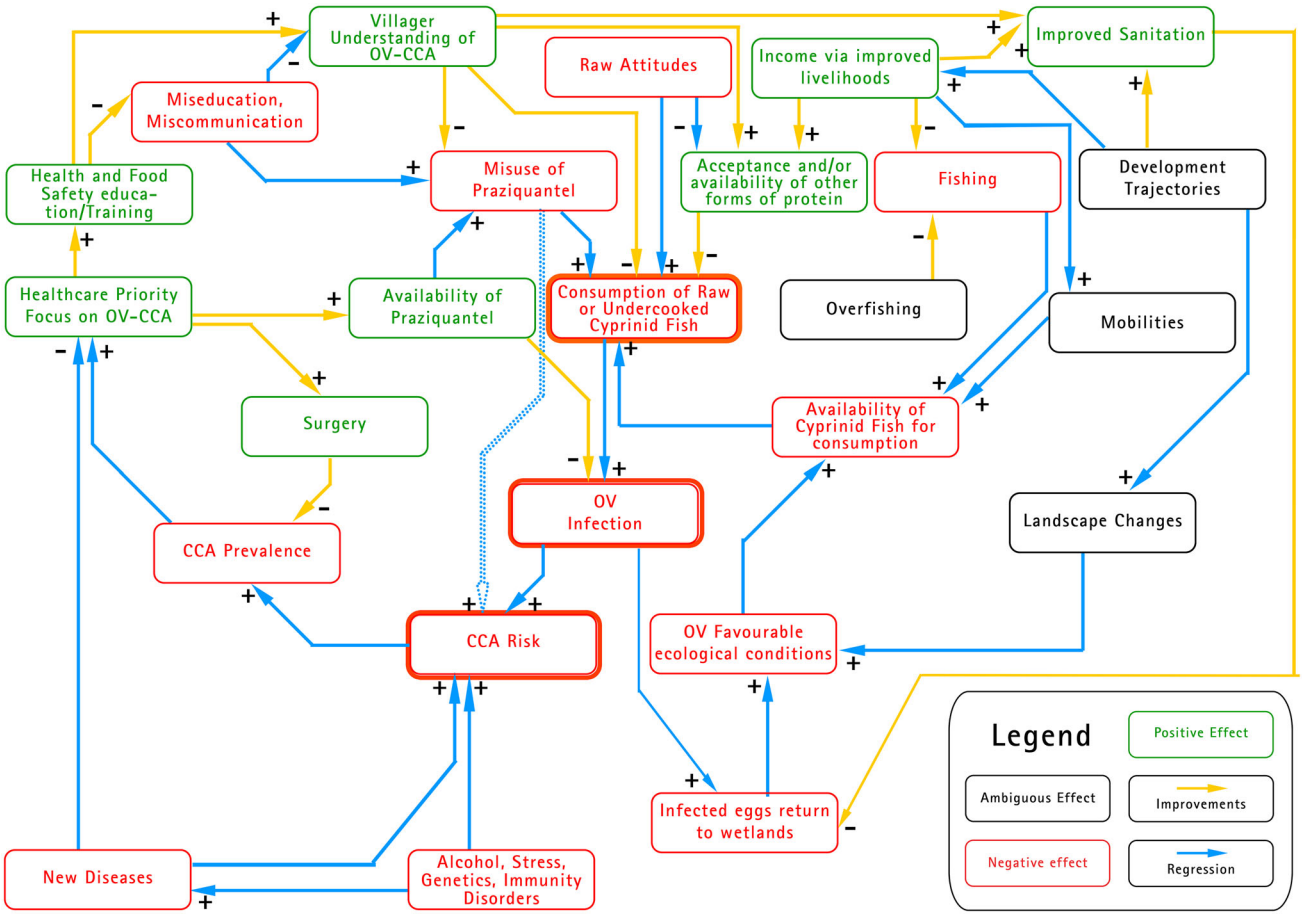

Figure 3. Causal loop diagram showing key human and environmental drivers of *O. viverrini* infection and cholangiocarcinoma prevalence. Causal loop diagrams are visualization tools in systems thinking, which is complementary to transdisciplinary research. Based on systems dynamics, arrows are labeled to indicate change (response variable increases are marked "+"; decreases "−") in response to an increase in the source variable, all else being equal. Of primary interest to the *O. viverrini*-cholangiocarcinoma issue is reducing consumption of raw or undercooked cyprinid fish (highlighted in *bold red*), because this behavior is the fundamental cause of *O. viverrini* infection, which in turn is an important risk factor for cholangiocarcinoma development (also highlighted). Variables colored *green* have largely a positive effect on reducing opisthorchiasis and cholangiocarcinoma risk; variables in *red* have a negative effect; variables in *black* have ambiguous outcomes. *Yellow arrows* represent changes that improve the situation; *blue arrows* represent changes that worsen the situation. The diagram indicates that the consumption of raw or undercooked fish can be reduced in two ways: (1) increasing acceptance and/or availability of alternative forms of protein (including cooked variants of potentially dangerous fish dishes), and (2) increasing villager understanding of the disease etiology and the risk factors. These linked "goals" can be achieved concurrently through clear and cogent health education, which may then diminish the effect of "raw attitudes" on health-endangering food practices (here a linkage is implied, but not shown in the diagram). To address the complex *O. viverrini*-cholangiocarcinoma health issue comprehensively, it is vital to recognize the entwined influences of ecological conditions, development measures, healthcare priorities and social-cultural phenomena, including ones not illustrated here (Color figure online).

cation has been instrumental in raising rural awareness of the *O. viverrini*-cholangiocarcinoma threat, but the degree to which most villagers, and healthcare volunteers, understand the problem is inadequate, potentially producing additional risk.

One reoccurring opinion in homestay interviews was that praziquantel can be consumed safely as many times as one believes is necessary (cf. Songserm et al. 2012; Phongluxa et al. 2013; Xayaseng et al. 2013). Given the easy access of praziquantel, some villagers regard the drug as a "health warrant," as praziquantel is often used to justify continued raw and fermented fish consumption habits (Grundy-Warr et al. 2012). Yet, recent research suggests that praziquantel is only a safe and appropriate treatment for *O. viverrini* infection the first time. For patients with chronic infection, repeated consumption may in fact increase the likelihood of liver cirrhosis and potentially cholangiocarcinoma development (Pinlaor et al. 2004,

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2008, 2009; but see Kamsa-ard et al. 2014). Consequently, those reliant on the worm-expelling functions of the drug for a sense of security may be unknowingly increasing their risk of developing cholangiocarcinoma probably from repeated exposure to infection.

At a broader level, a widespread but skin-deep understanding of the problem contributes to an overall perceived decline of the importance of *O. viverrini* infection. Exacerbating this perception is the rise of new health problems in rural areas, including obesity, cardiovascular disease and type II diabetes and cancers associated with urbanization and ''Westernization''—processes that are well underway throughout Thailand (Kosulwat 2002; Rigg and Salamanca 2011; Rigg et al. 2012). Increasingly, as these chronic diseases are perceived to be greater health threats than *O. viverrini* infection, priorities of national health education shift away from this issue. Importantly, the reduction in focus on *O. viverrini* affects the attention given to the training of village healthcare officials and volunteers, who may in turn miscommunicate health and safety information to villagers (Lee 2015). Although well-intended health education has the potential to disrupt the link between cultural food habits and the consumption on infected fish, (Ziegler et al. 2011), we found that if information is flawed or inaccurate, it may conversely obscure *O. viverrini* understanding at multiple levels, potentially increasing the risk of cholangiocarcinoma development.

We also observed how the level of *O. viverrini* infection risk may be increasing across time and space at various scales through contemporary landscape changes driven by rural infrastructural development and agricultural intensification. For example, in villages undergoing economic growth, the building of dams and irrigation systems (in support of agriculture intensification and modernized techniques) increases the extent and connectivity of habitats that support the complex *O. viverrini* ecological cycle (Ziegler et al. 2013; Sithithaworn et al. 2012b). These modifications could potentially increase intermediate host proliferation or their interaction with the various specific life stages of the parasite (shown in Figure 1). Such landscape modifications may also increase the presence of nourishment sources (a positive effect) or harmful contaminants in habitats (a negative effect), altering their suitability for *O. viverrini* (these influences are not indicated in the simplified diagram).

One prospective benefit of ongoing development is the building of modern sanitation systems that will ultimately reduce the return of *O. viverrini* eggs to wetland systems—a key mechanism that completes the *O. viverrini* life cycle. Yet, the potential role of improved waste management in reducing *O. viverrini* infection is currently offset by lingering practices of poor sanitation: defecating in paddy fields, direct disposal of wastewater in areas draining to surface water bodies, and poorly designed septic systems. Improperly designed or ineffective on-site sanitation systems are still prevalent, typically in the form of open-bottomed pit latrines. These are often preferred over government-sanctioned, close-bottomed systems, in large part because they are inexpensive to construct and require minimal maintenance. However, such systems enable wastewater, potentially containing *O. viverrini* eggs, to (re)enter wetland environments through interaction with subsurface water. The persistent prevalence of infection in Bithynia snails in endemic areas in Thailand and Lao PDR indicates active transmission (Kiatsopit et al. 2012; Namsanor et al. 2015).

An important consideration of promoting bottom-sealed septic tanks is that they require emptying more frequently than open-bottomed systems that drain freely and thus pose a recurrent cost to households. Financial considerations are also a strong determinant of how waste collecting firms or individuals eventually dispose of the accumulated refuse. For example, the waste collector who serviced several villages in the study area passed the sewage to farmers to apply on fields (e.g., cassava, rubber), or disposed of it in the forest.

Another critical human driver in *O. viverrini* transmission we observed was fishing. As a principal livelihood in the Isaan region, fishing provides the vital link between animal and human hosts by making infected fish accessible for human consumption. Overfishing can reduce availability in localized areas, but we observed stronger effects from the expansion of fish market networks. With growing demand for export of fresh or fermented fish products to areas located away from wetlands, fishermen are compelled to transport their catch across greater distances, a motivation made possible by increasing development of transport networks and refrigeration (preservation) facilities. Although these improved ''mobilities'' contribute to better individual livelihoods, they may also increase the geographical extent and/or intensity of *O. viverrini* infection risk, even in locales where ecological conditions are unfavorable for the life stages of the parasite.

Although shifts away from agriculture-based livelihoods and fishing may improve household ability to afford

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alternative types of protein, they may not necessarily reduce risk for *O. viverrini* infection, because of the enduring preference for dishes made with raw or undercooked fish. In some of our more developed study sites, we observed that rising income brackets simply led to villagers switching from being producers to consumers in their local fish commodity chains, with high consumption of fermented fish products in particular being retained. In essence, the regional idiosyncrasy of culturally seated raw attitudes constitutes a developmental wild card, creating inertia in culinary habits and food preparation techniques, even as migration patterns, livelihood transitions and other social changes occur as expected. Here, we use the contentious phrase "raw attitudes" (Grundy-Warr et al. 2012), because it reinforces the remarkable strength of local food traditions in the area—traditions that we learned to be creative, complex and important for maintaining strong community bonds. Such ties are a strong positive determinant of psychosocial health, to some extent possibly even countering cancer development risk.

This diagram represents some of the nuanced ways by which we now perceive the complex *O. viverrini*–cholangiocarcinoma relationship, which is connected with culture, rural life, development trajectories, healthcare priorities, education, hydrology and ecology. In such a social ecological system, the collective influence of these factors on *O. viverrini*-cholangiocarcinoma pathology may be overlooked by research that is too narrowly focused on particular aspects in isolation (cf. Parkes et al. 2005).

Outlook

The investigation has given us a clearer view of the possibilities and challenges that lie ahead in addressing persistence of *O. viverrini* infection and cholangiocarcinoma in the Mekong region. We see a need for further investigations attuned to the region's socioeconomic circumstances and unique food culture to better understand the diverse factors influencing eating behavior. In doing so, a key consideration is how to meaningfully incorporate principles of "community engagement" (Parkes and Panelli 2001; Murphy 2014). Here, we stress that simply conducting activities in a village does not constitute deep and meaningful villager engagement or cooperation. In our case, new insights were made possible because the students lived among villagers, participating in local practices and engaging with families on a deeply personal level. This connection enabled them to shed the "outsider looking in" position that frequently prevents research subjects from speaking truthfully when interviewed by researchers who appear to be judging them—a research issue particularly relevant to the *O. viverrini*-cholangiocarcinoma problem, because past eradication efforts have at times invoked power and authority to enact behavioral change.

Looking ahead, there may be a need for a shift in research mindsets and methods, combining top-down and bottom-up approaches to better engage with human desires, tastes, beliefs and memories (Lee 2015; also see de Albuquerque Possas (2001) on social ecosystems health). Importantly, this critical health issue must be understood as embedded within socially driven networks that are deeply influenced by resource-dependent livelihoods (cf. Breilh 2003). Parkes et al. (2005) called attention to the imperative of designing research and responses that are commensurate with understanding the complex social and ecological contexts in which infectious diseases occur. To do so one must frame the problem through a pluralistic approach, in which knowledge and perspectives from different academic and non-academic disciplines are merged. This call is fitting for the *O. viverrini*-cholangiocarcinoma issue, as the region's unique sociocultural and environmental circumstances often vary between neighboring districts or even villages (Sripa et al. 2015).

Further, there is a need to contextualize these actions within broader processes of development—particularly those that implicate livelihoods and land-use through agricultural policy, water and waste management, and transportation infrastructure. By situating health outcomes in changing social, economic, ecological and biophysical conditions, healthcare and research initiatives can be kept relevant, flexible and sensitive to local changes over time (cf. Parkes et al. 2005). At present, implementation guidelines and explicit operational criteria for such approaches are lacking (Nguyen-Viet et al. 2015; Richter et al. 2015).

The multiple perspectives offered by transdisciplinary approaches may be invaluable for reorganizing healthcare frameworks to incorporate dynamic and non-medical constituents of disease. Albrecht et al. (2001) state that transdisciplinary approaches are the most capable of coming to terms with health problems that are embedded in complex causal connections (cf. Rosenfield 1992). This is especially important for issues like the *O. viverrini*-cholangiocarcinoma puzzle in northeast Thailand, where convoluted human–ecological interactions enable these diseases to persist, despite longstanding, active health education and interventions. Successfully applying such

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approaches is likely to be methodologically challenging to any complex healthcare problem (Parkes et al. 2005). Nonetheless, it remains vital to strive for holistic understandings of complex health problems in order for research to guide the formulation of grounded, cogent and impactful health solutions.

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