

UC Berkeley

UC Berkeley Previously Published Works

Title

Modeling liver fluke transmission in northeast Thailand: Impacts of development, hydrology, and control

Permalink

<https://escholarship.org/uc/item/17j1q5n9>

Journal

Acta Tropica, 188

ISSN

0001-706X

Authors

León, Tomás M

Porco, Travis C

Kim, Christina S

et al.

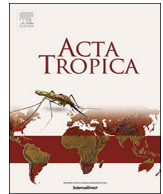
Publication Date

2018-12-01

DOI

10.1016/j.actatropica.2018.08.008

Peer reviewed



Modeling liver fluke transmission in northeast Thailand: Impacts of development, hydrology, and control

Tomás M. León^{a,c,*}, Travis C. Porco^b, Christina S. Kim^c, Sasithorn Kaewkes^c, Wanlop Kaewkes^c, Banchob Sripan^c, Robert C. Spear^a

^a School of Public Health, University of California, Berkeley, USA

^b University of California, San Francisco, USA

^c Tropical Disease Research Center, Khon Kaen University, Thailand

ARTICLE INFO

Keywords:

Liver fluke
Opisthorchis viverrini
Mathematical modeling
Water-related transmission
Thailand

ABSTRACT

Human infection with the Southeast Asian liver fluke *Opisthorchis viverrini* and liver fluke-associated cholangiocarcinoma cause significant disease burden in Southeast Asia. While there has been considerable work to understand liver fluke pathology and to reduce infection prevalence, there remains a limited understanding of the environmental determinants of parasite transmission dynamics to inform treatment and control programs. A particular setting where targeted control efforts have taken place is the Lawa Lake complex in northeast Thailand. Here, we describe the recent history of host infections, as well as the hydrologic characteristics of this floodplain ecosystem that influence the extent of snail habitat and fish mobility and the transport of human waste and parasite cercariae. Using mathematical modeling, we outline a framework for reconstructing environmental transmission of *O. viverrini* over the course of the Lawa Project control program from its inception in 2008 until 2016, using locally acquired but fragmentary longitudinal infection data for both humans and environmental hosts. The role of water flow in facilitating movement between snail, fish, human, and reservoir hosts is a particular focus with respect to its relevant scales and its impact on success of interventions. In this setting, we argue that an understanding of the key environmental drivers of disease transmission processes is central to the effectiveness of any environmental intervention.

1. Introduction

Human liver flukes are waterborne parasites that cause significant disease burden, particularly in Asia. Specifically, they are foodborne trematodes, which some researchers have labeled as “among the most neglected of the so-called neglected tropical diseases” (Keiser and Utzinger, 2009). Liver fluke species include *Clonorchis sinensis*, *Opisthorchis felinus*, *Opisthorchis viverrini*, *Fasciola hepatica*, and *Fasciola gigantica*. The species of specific interest here is *O. viverrini*, the Southeast Asian liver fluke. *O. viverrini* and *C. sinensis* are both classified as Group 1 carcinogens by the International Agency for Research on Cancer for triggering and being associated with bile duct cancer, known as cholangiocarcinoma (CCA), which has poor prognosis and a high fatality rate (WHO, 2012; Sripan et al., 2011, 2012). Opisthorchiasis, infection with the Southeast Asian liver fluke, and clonorchiasis, infection with the related Chinese liver fluke, are neglected tropical diseases with a combined at-risk population numbering approximately 700 million (Sithithaworn et al., 2012). Morbidity from opisthorchiasis and

clonorchiasis typically occurs due to high worm burden, making infection intensity an important predictor of disease burden and risk of CCA (Sithithaworn and Haswell-Elkins, 2003).

O. viverrini is a primary parasite of interest and a public health priority in Thailand, where it is transmitted to humans via the consumption of popular local raw and fermented fish dishes such as *koi pla* and *pla som*. Initial surveys in the 1950s in northeast Thailand revealed near 100% human prevalence of *O. viverrini* infection in some districts (Sithithaworn et al., 2012). Regionally, the estimated prevalence dropped from 64% to 35% in the 1980s (Jongsuksuntigul and Imsomboon, 2003). It has since fallen even more, stabilizing at approximately 16% as reported in two surveys carried out in 2000 and 2009 (Sithithaworn et al., 2012). Nonetheless, high-risk villages and districts still see infection prevalence levels up to 60–70%. The highest prevalence of opisthorchiasis and CCA are found in northeast Thailand, including in the area surrounding Khon Kaen (Sithithaworn et al., 1997; Sriamporn et al., 2004).

Through research done at Khon Kaen University (KKU) and other

* Corresponding author at: School of Public Health, University of California, Berkeley, USA.

E-mail address: tomas.leon@berkeley.edu (T.M. León).

<https://doi.org/10.1016/j.actatropica.2018.08.008>

Received 14 April 2018; Received in revised form 17 July 2018; Accepted 8 August 2018

Available online 24 August 2018

0001-706X/ © 2018 Elsevier B.V. All rights reserved.

institutions, a greater understanding of the lifecycle of *O. viverrini* is being achieved, but infection prevalence in humans remain relatively high in some areas despite prevention and control activities. While the pathologies of opisthorchiasis and CCA have been extensively studied, there is limited literature addressing the ecological and hydrological aspects of parasite transmission in the environment (Wang et al., 2017; Grundy-Warr et al., 2012). Here we examine the spatial and temporal history of infection in the Lawa Lake ecosystem surrounding Khon Kaen, with a long-term objective of estimating the differential effects of development, control activities, meteorological factors, and hydrologic flows on the recent history of disease prevalence in humans, snails and fish.

Lawa Lake is an approximately 4000-acre body of water that is highly vegetated and subject to significant hydrologic changes caused by seasonal variation in northeast Thailand. A peak in liver fluke infections is seen with lag following the rainy season in Thailand, as flooding facilitates the spread of fecal contamination and coincides with the rapid increase in snail populations (Sithithaworn et al., 1997). Since several weeks are required for the parasite to mature through its life stages, high infection rates in fish are seen in the late rainy season and summer (July–January). Low infection burdens occur in the dry season and summer (March–June). A primary industry on the lake is fishing, which contributes to the environment mediating ongoing liver fluke transmission in the local area (Aunpromma et al., 2012). The hydrology of the Lawa Lake region is exceedingly complex and disturbed, as significant changes have occurred in recent years due to construction of new irrigation canals and ditches, new culverts and spillways that are opened and closed in the flooding season (Fig. A1), and fish ponds that have become increasingly popular as a source of food and revenue.

The Lawa Project, initiated in 2008 in the villages around Lawa Lake, is described in detail in Sripa et al. (2015). By 2016, Lawa Project public health control programs had contributed significantly to reducing infection levels in most villages to 10–20% from baseline prevalence values of up to 74%, contingent upon regular screening and treatment of villagers. The program included intensive health education of villagers, technical training of health staff and volunteers, school-based curriculum, and disease surveillance, a multicomponent approach to preventing and controlling the spread of *O. viverrini*. It is currently unknown what the contribution of each of these components was, or how the results compared to a single intervention or a standard mass drug administration campaign. There is increasing interest in the benefits or lack thereof in multi-pronged public health interventions, particularly those that target the same exposure pathways (Luby et al., 2018).

The life cycle of *O. viverrini* is complex, including snail and fish intermediate hosts and reservoir hosts such as cats and dogs (Fig. A2). An understanding of the ecological situation underlying parasite transmission informs successful environmental control and helps to identify optimal timings and locations for intervention. Herein we look at each step of the transmission process and how it occurs in the environment and then discuss the available data and mathematical model for *O. viverrini* transmission.

2. Ecological theory

2.1. Human-to-snail linkage

The human-to-snail transmission process requires that *O. viverrini* worms within an infected human or reservoir host are actively shedding eggs, which can number in the thousands per day (Petney et al., 2013). Such shedding does not occur at a constant rate and, in cases of extreme worm burden, bile duct obstruction in humans may be so severe that eggs cannot be released into the intestinal tract. Safe sanitation is sufficient to treat human waste and render the eggs unviable; however, not all people have access, and other practices can bypass proper treatment. In the Lawa Lake complex, where the vast majority of villagers have

improved sanitation, fecal waste may enter the environment either by open defecation by farmers and fishermen or via septic trucks pumping out waste from sealed latrines and applying it untreated onto agricultural fields for crop fertilization or into open bodies of water. These means of bypassing proper sanitation potentially injects millions of *O. viverrini* and other fecal-related parasite eggs into the environment on a regular basis.

After release into the environment, the egg-containing feces are likely to have reached active *Bithynia* snails, which consume the eggs. Egg viability is estimated to last a month, limiting the success of this process (Echaubard et al., 2017). Hydrologic data allows us to describe potential and active *Bithynia* snail habitat in proximity to infected humans and reservoir hosts. The location of such habitats changes seasonally in monsoon-influenced climates, like that of northeast Thailand. Hydrologic data can also help us understand the linkage between the release of egg-containing feces into the environment and their contact with snails. As the eggs are not motile, any mobility is due to water flows, such as from rainfall, rice field irrigation, or river and lake currents. Modeling this hydrologic activity may help predict fate and transport of parasite eggs.

2.2. Snail-to-fish linkage

The snail-to-fish transmission process occurs after the egg has hatched into a miracidium and matured through the sporocyst and rediae stages into cercariae. Research suggests that this process takes on average 30 days before viable cercariae can be released (WHO, 2012). The snail must survive this pre-patent period without being killed by the parasite or other means (WHO, 2012). The snail needs an aqueous or amphibious habitat, which may not persist locally, especially in the dry season. When the cercariae are released, they have been estimated to have 24–48 h to find and penetrate a susceptible fish host. However, in the laboratory, experimentally released cercariae appear to become moribund after just a few hours, suggesting that this window may be even narrower. Because older and more developed fish are fairly resistant to cercarial penetration, the targeted fish should be fish fry or very young fingerlings before their scales have fully developed and provide greater resistance to the *O. viverrini* cercariae. This process requires that the snails dwell in close proximity to fish spawning and that the cercariae are released when the fish are hatched but not yet mature. This results in a small spatiotemporal window, somewhat offset by the large quantity of cercariae (in the thousands) that can be released by a single snail. Most snail surveys find snail infection prevalence to be 0.2% or below, even when human infection prevalence is greater than 50%. Consequently, fish spawning sites likely only have a few infectious snails in their vicinities. When the cercariae encyst, they become metacercariae, and wild fish have been found to contain up to hundreds of metacercariae (Pinlaor et al., 2013; S. Kaewkes and W. Kaewkes, unpublished data). Evolutionarily, this process allowed the bioaccumulation of the parasite in the fish host to bypass the difficulties of contact between snails and susceptible definitive hosts, as in the case of schistosomiasis. Hydrology is important in this linkage because of the potential for flows to increase the range where cercariae might contact susceptible spawning cyprinid fish. This linkage expands the zone from a radius of a few meters to tens or hundreds of meters, depending upon meteorological and landscape factors, resulting in an exponential increase in spatial hotspot area where possible transmission occurs.

2.3. Fish-to-human/cat/dog linkage

This transmission process requires that the fish survive to maturity to be eaten by a definitive host after being caught by a fisherman. Cats and other reservoir hosts may catch and consume some infected fish, but no published study has yet documented or quantified whether or to what degree this at-risk behavior occurs. Since fish become infected at a small size and age, they must mature and survive long enough to be

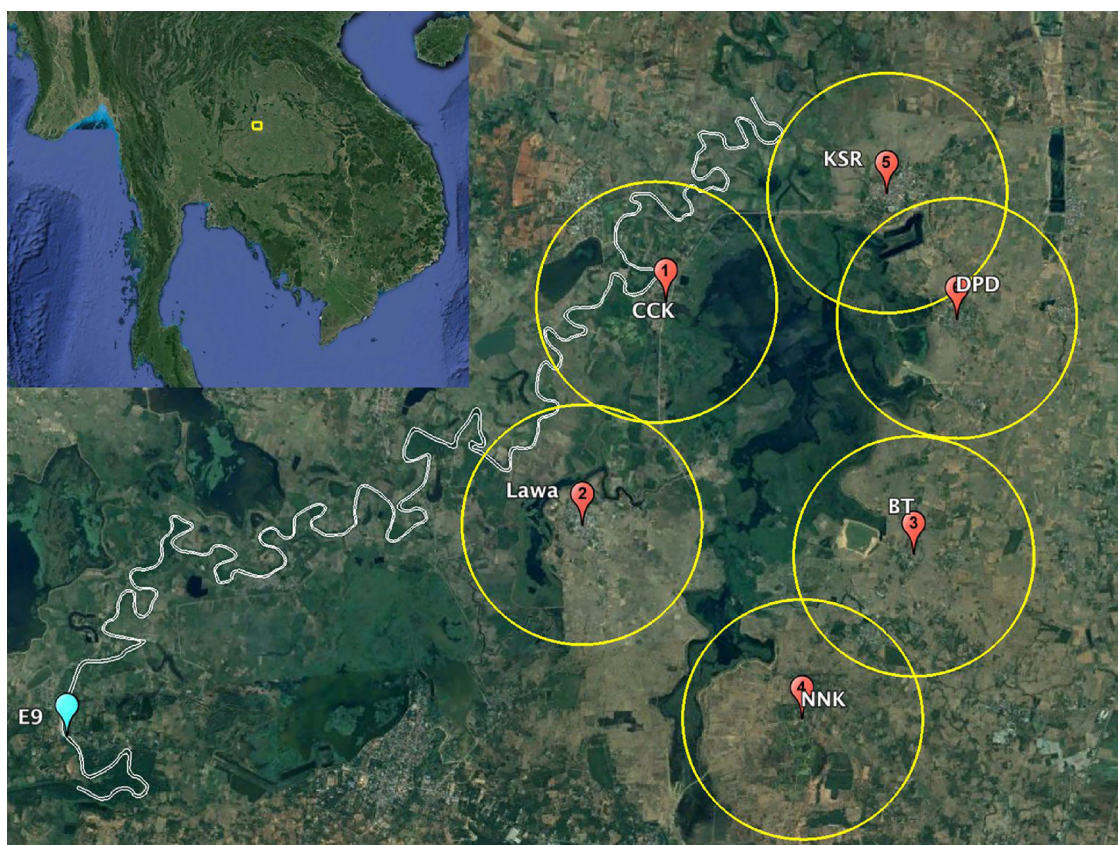


Fig. 1. The six village clusters surrounding Lawa Lake with 2 km radius buffers, also showing the Chi River and the E9 gauge (Google Earth Pro).

marketable. However, they are caught and eaten even at small sizes (Kim et al., 2016). Next, some fraction of caught and consumed fish is cooked or fermented long enough to inactivate liver fluke metacercariae, and the remaining fraction accounts for the relevant exposure to humans and reservoir hosts. Since fish scraps fed to cats and other animals are highly unlikely to be cooked, these account for a disproportionate risk for growth into adult worms. Once infected fish are consumed, the metacercariae have to excyst and successfully migrate to the bile ducts, where they will mature into adult worms. In a hamster model, the proportion of successful conversion is approximately 55% (Onsurathum et al., 2016). Hydrology matters here in its influence on fishing patterns and fish mobility. Fish spawning in isolated, unfished bodies of water are unlikely to be eaten by relevant host species.

3. Material and methods

3.1. Local data

Our studies in the Lawa area utilize data collected in the period between 2008 and 2016, focusing on six villages or adjacent groups of villages and their surroundings as shown in Fig. 1 (Berkeley IRB Protocol # 2014-06-6463). Their hydrological setting is dominated by Lawa Lake, which receives three separate input flows of water: two from upstream watersheds to the southwest and southeast, and one from the Chi River, which runs in close proximity to the west and north of the lake. The river regularly floods its banks in the wet season, creating a wetland between the river and the lake that often inundates the villages (CCK, notably) located in between. Historically, infection with *O. viverrini* has been the highest in the villages south of the lake, with NNK at 74% prevalence in 2008. Table 1 shows the infection prevalence and intensity from 2008 to 2012. These data derive from surveys coordinated with control programs conducted by KKU. Human infection surveys typically reached approximately 10–20% of a village's

Table 1

Infection prevalence (%) and intensity (eggs per gram, EPG) for six village clusters around Lawa Lake.

Village Cluster	2008	2010	2012
CCK	54.9% (593)		44.3% (139)
Lawa	67.1% (501)	63.1% (108)	
BT	61.9% (346)	37.2% (131)	35.0% (136)
NNK	74.1% (499)		50.0% (61)
KSR	16.4% (101)		
DPD	22.1% (112)	36.5% (82)	

population, recruited based on consent to participate in the studies. All positive cases were treated with praziquantel. However, participants were not randomized, and in some cases individuals participated in more than one annual survey. Partial data shows between 38% and 57% of individuals in villages with multiple surveys were part of more than one survey. Resampled individuals only had slightly lower prevalence levels than those who were not, but the results differed by only a few percentage points in most cases. The vast majority of follow-up cases had markedly lower average intensity, measured in parasite eggs per gram (EPG) of feces. These findings point to the likelihood that the at-risk behavior of raw or undercooked fish consumption continued after the first survey and treatment and that burden builds up over a period of years.

Decreases in human infection prevalence over time can be seen in four of the six village clusters. KSR yielded no follow-up data, and DPD actually showed an increase. EPG values drop by about an order of magnitude in the 2008–12 interval, but not uniformly. Considering the two village clusters that yielded data from 2008, 2010, and 2012 (Lawa and BT), we find that in Lawa EPG drops by a factor of approximately 30. However, in BT average EPG value declined by only a factor of approximately 2.5, with minimal drop between 2010 and 2012. The

data for other villages is less complete, but generally suggest decreased intensity in infected individuals, though the trend is far from linear. The most recent data available to us is from local clinic surveys conducted in 2015 and 2016 in five of the village clusters; prevalence values ranged from 9 to 15%, though these surveys are based on one sample rather than multiple as in the 2008, 2010, and 2012 surveys. EPG values were not available, but the general picture is one of continued transmission, but at much reduced levels of both prevalence and intensity in humans from the 2008 baseline levels.

The reductions in human infection are also reflected in recent environmental data. The most thorough study of the environmental conditions in the Lawa area linked to this infection pattern is that of Kim et al. (2016), who found in 2013–2014 geographically widespread paucity of infected snails and fish. There was continued evidence that the southernmost village clusters in the Lawa system supported higher levels of transmission though, as earlier data demonstrates more clearly. One environmental justification for this pattern that they made was “a nitrogen-salinity gradient where higher levels in the lake's southern region predicted higher *Bithynia* relative abundance and lower snail and fish species diversity.”

Changing agricultural practices and other development have modified the environment to meet water management needs in the area. Fig. A1 shows the hydrologic structures of relevance that existed in 2016. Some of these structures were constructed between the start of the control program in 2008 and 2016. This construction has altered the impacts of flooding on the surrounding environment. Precipitation has also varied widely from year to year in this time period as demonstrated in Fig. 2. Fig. 3 shows the monthly response to this rainfall pattern over the same period at gauge E9 on the Chi River, which is the closest and most relevant gauge to the Lawa Lake complex.

In addition to the complexities of the hydrologic system in this region, *O. viverrini* exhibits a complex transmission cycle, as previously described. While the structure of the cycle is well understood, that alone is insufficient to understand the importance of certain characteristics of places and populations that contribute to infection and thereby are targets for effective interventions. In this context, mathematical models have been used in studying various aspects of infectious disease transmission, most commonly to assess the effects of mass drug administration strategies (Anderson et al., 2014; Anderson and Basañez, 2016). Modeling has been less commonly applied to study the

environmental determinants of infectious disease transmission, but for diseases like opisthorchiasis, the approach provides a platform for the integration of disparate information relevant to understanding the potential of non-medical interventions (Michael and Gambhir, 2010; Cheng et al., 2016).

3.2. Mathematical modelling

We elaborate upon and modify a differential equation model derived from Boerlage et al. (2013), adapting this model to describe the aforementioned structure. Using this model, we integrate quantitative data available to estimate rates of transmission of the various forms of the parasite between the four populations involved. The Boerlage model is a deterministic compartmental SI model for fishborne zoonotic trematodes, a class of parasites that includes liver flukes. There are four state variables: humans (H), mammalian reservoirs (R) including cats and dogs, snails (S), and fish (F). The modified equations are given in the Appendix; we expanded the model to account for the spatial/metapopulation structure of the Lawa Lake complex in the multi-village form. We have distilled the number of parameters based on lack of available data for *O. viverrini* specifically into a single transmission parameter β per process because of the great uncertainty around values used in the original Boerlage model; parameter values used are listed in Table A1. The single-village form of the model assumes each village has unique populations of the four host states but neither imports nor exports parasites to other villages. Hence, the simulations of transmission using the single-village model are aimed at exploring the plausibility of the assumption that all transmission between the infected populations are restricted to be within the village and its immediate hydrologic environment.

For the base case presented here, we excluded reservoir host populations due to limited local data relevant to their contribution to the transmission cycle. The same model run with reservoir host populations included produces similar dynamics, only with increased fish prevalence values for BT. Human population values N_H were set based on data provided by the village clinics around baseline (2008). Human population sizes are assumed to remain constant over time, because of minimal changes over the timespan of simulation. Two parameters difficult to estimate were the snail and fish populations, N_S and N_F , respectively. Methods for estimating fish populations are inexact, and

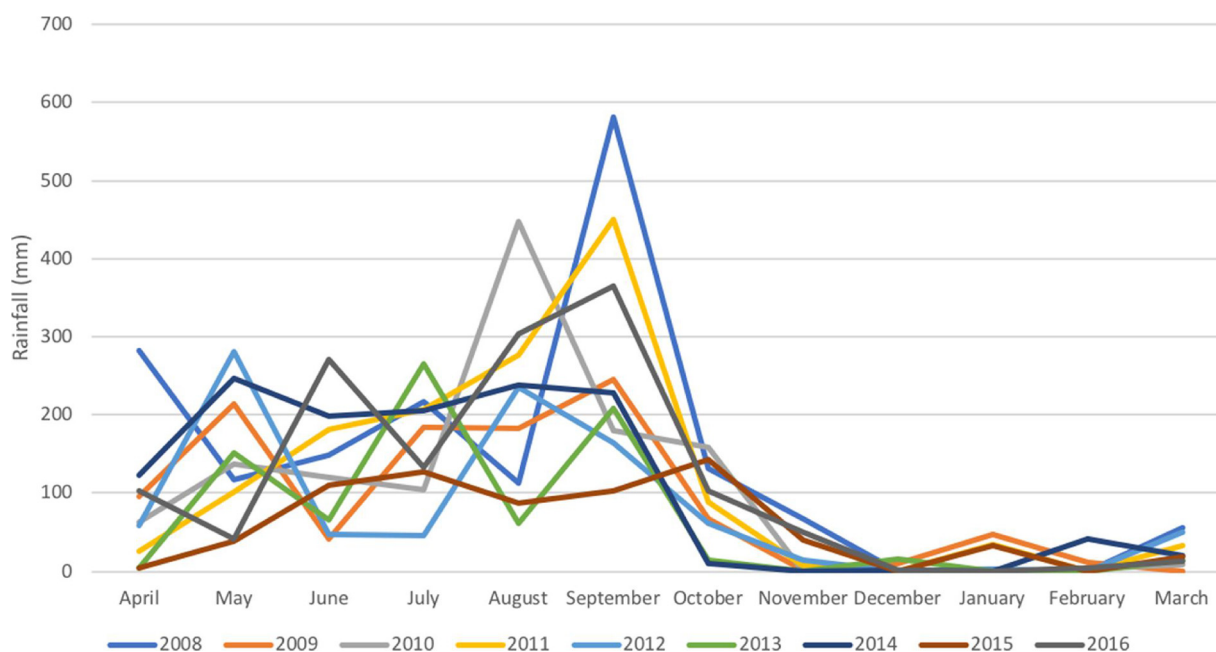


Fig. 2. Rainfall in Khon Kaen Province by Month, 2008–2016.

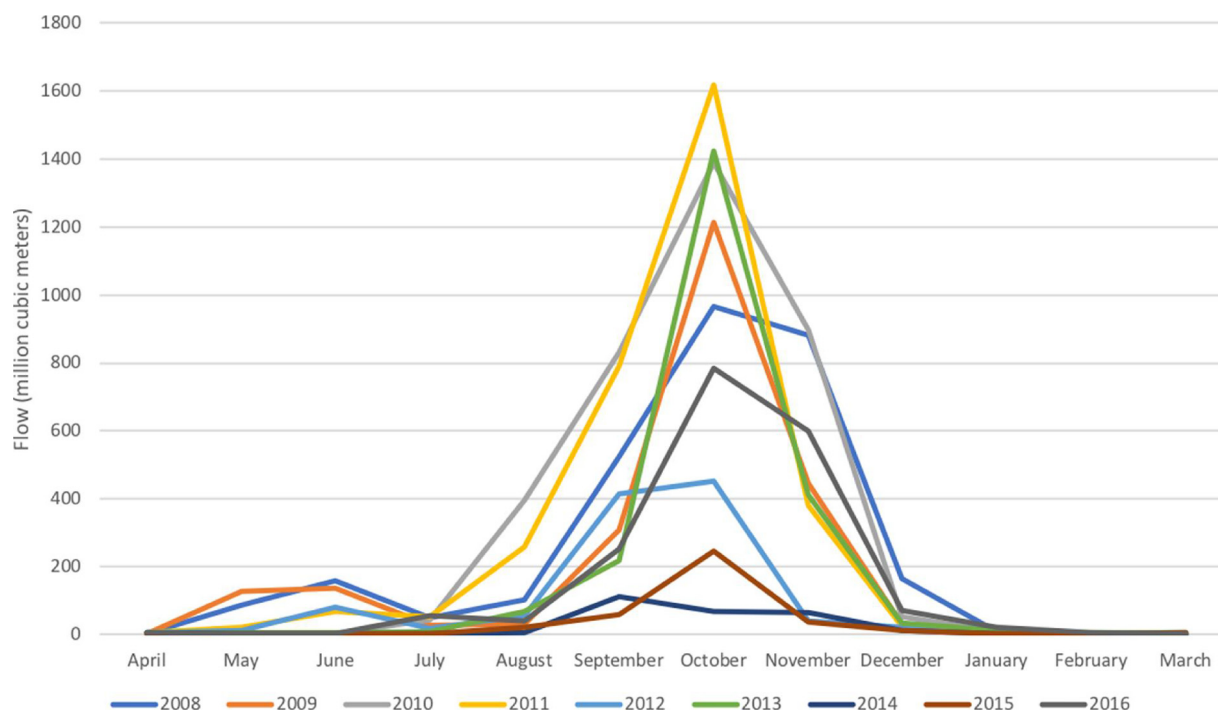


Fig. 3. E9 Gauge Flow by Month, 2008–2016.

subject to landscape heterogeneities such as those in the Lawa Lake system (Kim et al., 2016; Wang et al., 2017). Beyond estimating the total fish population relevant to a village, for the model the partition of the total that is susceptible to *O. viverrini* needs to be determined. While some capture and diet data hints at this proportion, spatial differences are not known or understood, so a partition parameter has not been applied in this model. For snail populations, the challenge increases because of competition between snail species, some susceptible to infection and some not. *Bithynia* snails tend to congregate in high densities in some habitats and be completely absent from others, so the spatial heterogeneities are consequential. Results from hydrologic modeling that better elucidate extent of viable habitat for both types of hosts will improve our estimation of N_S and N_F . For the preliminary runs of the single village model reported here, we assumed $N_S = 30,000$ and $N_F = 3000$, a ratio of 10 snails:1 fish. On the village scale, a better estimation is complicated by determination of what extent of host habitat is relevant to the liver fluke transmission cycle. Relevant habitat would overlap between villages, and how to most realistically partition or account for their contributions to each village's transmission is difficult.

Considering initial conditions for snail and fish prevalence values, we utilized snail and fish survey data from 2008 (S. Kaewkes and W. Kaewkes, unpublished data). For snail initial prevalence values, we have set the initial value at 0.2% prevalence for all villages. This is consistent with snail surveys from 2008 but ignores heterogeneities between villages because of the lack of sufficient data to substantiate any differentiation. Nonetheless, extent of snail hotspot areas would contribute significantly to transmission potential for affected villages.

There are significant uncertainties in the local data and inherent variability of the parametric estimates from the literature. Nonetheless, this modeling exercise represents an initial effort for compiling available knowledge to best understand environmental transmission and reconstruct historical trends in infection prevalence. We anticipate these patterns will be better elucidated when hydrologic data is integrated into the modeling schema. At this point, however, we are also interested in the patterns of response within village clusters. With these caveats, the three parameters remaining to be estimated in the single village model are β_{FH} , β_{HS} , and β_{SF} , which govern the transmission

between the different host stages internal to each village cluster. Specifically, in contrast to Boerlage et al. (2013), wherein the r parameters govern the likelihood of a single parasite (whether egg, cercaria, or metacercaria) causing successful infection in the next stage host, β governs the likelihood of successful transfer of parasitic infection given contact between two hosts in consecutive stages of the transmission cycle.

4. Results

Table 2 contains the values of the β model transmission parameters that were used in simulation runs. These model parameters could not be estimated from field data or the literature, so the first set of estimates for these parameters was obtained by assuming that the system was in equilibrium in 2008. Simulation results under this assumption (of equilibrium in 2008) are shown in the Appendix (Fig. A3). The patterns produced by the model using these parameter estimates do not match the field data. For example, human prevalence bounces back quickly after praziquantel treatment as expected due to the small number of those diagnosed and treated, and fish prevalence remains largely unchanged. Snail prevalence declines in most villages but remains substantially higher than reported values.

Table 2
Beta transmission parameters for single village model.

	CCK	Lawa	BT	NNK	KSR	DPD
Equilibrium						
Fish to Human	2.50E-10	7.24E-11	2.53E-10	1.81E-11	3.32E-07	2.68E-07
Human to Snail	8.90E-09	1.01E-08	4.92E-09	8.92E-09	6.56E-12	1.18E-11
Snail to Fish	7.34E-06	7.10E-06	3.40E-06	8.96E-06	1.67E-05	1.35E-05
MCMC						
Fish to Human	2.95E-07	3.45E-07	7.26E-07	2.28E-07	3.30E-08	7.75E-08
Human to Snail	1.25E-08	2.53E-09	3.45E-09	2.26E-08	1.28E-08	1.48E-08
Snail to Fish	4.48E-06	7.03E-06	2.23E-06	2.28E-05	7.08E-06	3.89E-06

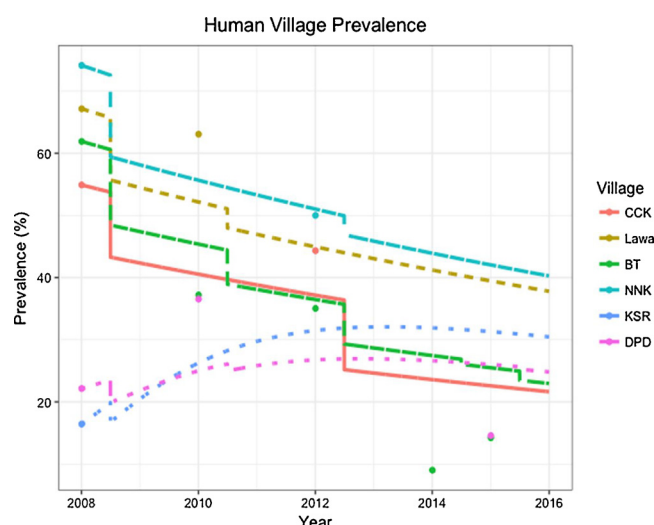


Fig. 4. Single village model with human infection survey data.

Table 3
Simulated human prevalence values for single village model.

	2008	2012	2016
Equilibrium			
CCK	54.9%	47.0%	39.7%
Lawa	67.2%	57.9%	60.6%
BT	61.9%	48.5%	44.6%
NNK	74.1%	66.4%	67.7%
KSR	16.4%	13.7%	13.9%
DPD	22.1%	17.9%	17.8%
MCMC			
CCK	54.9%	37.2%	21.6%
Lawa	67.2%	45.0%	37.8%
BT	61.9%	36.5%	23.0%
NNK	74.1%	51.0%	40.3%
KSR	16.4%	31.5%	30.5%
DPD	22.1%	17.9%	17.8%

A second set of β parameter values, shown in Table 2, was estimated using a Markov Chain Monte Carlo (MCMC) procedure (Metropolis-Hastings algorithm) for the model output to fit the three transmission parameters between each host using the equilibrium values as priors and with a long burn-in period. Fig. 4 shows the model run output using the MCMC-derived values with data points from the human infection surveys (additional graphs in Fig. A4 in the Appendix). To fit these values, additional prevalence points were used from local surveys in 2014 and 2015 for some of the village clusters. Table 3 lists the simulated disease prevalence estimates for human infection in 2008, 2012 and 2016, which match up with the human infection surveys. There are marked differences in the equilibrium vs. MCMC estimates between the northern and southern village clusters, particularly in the fish-to-human values, which require much lower “success” (by several orders of magnitude) in transmission in southern villages to account for the decrease in human prevalence. However, although the MCMC estimates result in better fits to the field data in the 2008–2012 period as shown in Fig. 4, the predicted 2016 prevalence levels remain well in excess of those observed. From these simulations, it seems clear that either control activities were very effective in diminishing consumption of infected fish or meteorological and hydrologic factors during these years substantially reduced transmission between hosts and/or between villages.

5. Discussion

An important issue for this analysis is the relative contribution of

different factors to the decrease in infection prevalence and intensity among human, snail, and fish host populations. Based on the individual-village model framework described, deterministic simulations could not replicate the drops shown in field survey data, which far outpaced the effects of documented treatment with praziquantel and worm mortality. Several questions remain. The fragmentary and limited nature of the infection surveys could have misrepresented the true population infection status through sampling bias and methodologies, which may have been more likely to include infected humans but less likely to find infected snails and fish, thus thwarting the ability of surveys and modeling simulations to accurately capture the dynamics. The significant role of hydrology was not accounted for but changes in irrigation, agriculture, aquaculture, and other aspects of development clearly disturbed and changed the environment between 2008 and 2016. In addition, spillover effects related to screening and health education in the Lawa Project control programs could have contributed to unobserved use of praziquantel and changes in diets, which would also account for the unexplained drops in prevalence between 2008 and later surveys. Some combination of these factors is likely, so it is worthwhile to attempt to parse out each one's relative contribution and impact on transmission potential to better design infectious disease treatment and control programs, as in the case of opisthorchiasis in northeast Thailand. If the historic patterns of infection prevalence are adequately replicated by an expanded model, scenario analysis incorporating these additional factors could be useful for simulating impacts of different control and treatment strategies and environmental variables.

Synthesizing diverse and fragmentary data poses many challenges but is important to understanding infectious disease transmission in complicated circumstances. Recent studies have highlighted that even “simple” exposure pathways do not easily yield to treatment and control strategies (Luby et al., 2018). In developing contexts, the influence of increasing individual and state wealth is likely to precede or at least coincide with “big data” approaches that provide opportunities to gain better sources of environmental and epidemiologic data for use in modeling. Yet, infectious diseases will continue to disproportionately impact the poor and resource-limited contexts (Hotez, 2017). Models can be useful for leveraging available but incomplete data to better inform environmental control strategies and interventions coupled with treatment and clinical approaches.

6. Conclusions

We have added to the limited literature modeling liver fluke transmission with particular attention to the context of a lake system in northeast Thailand with historically high prevalence of parasite infection and incidence of subsequent cancer. By using available data, we have reconstructed changes in environmental transmission in the past decade. Based on our results, the decrease in prevalence is unlikely to be due solely to praziquantel treatment but as a result of changes in the environment and eating behaviors. An unusually wet period between 2008 and 2011 and changes to the hydroscape via more intensive irrigation, increased aquaculture, and flood management all impacted how the parasite and its hosts moved in the environment. These insights support increased attention to hydrological and ecological changes and their impacts on disease transmission, whether related to something as big as a dam or as small as a culvert. Estimating the relative contribution of key drivers can inform design and implementation of more effective treatment and control programs that are timed and targeted based on modeling results. Our next objective is to implement a meta-population version of the transmission model and inform the larger set of transmission and connectivity parameters with seasonal variation in the hydrologic conditions of the Lawa Lake complex.

Competing interests

The authors declare they have no competing interests.

Acknowledgments

Thanks to Sutasinee Sripa and Sangduan Wannachart for assistance with translation and data collection.

This material is based upon work supported by a US National Institutes of Health (NIH) grant [R21AI104513] (TML and RCS) and by the National Science Foundation Graduate Research Fellowship under Grant No. [DGE 1106400] (TML).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.actatropica.2018.08.008>.

References

- Anderson, R., Truscott, J., Hollingsworth, T.D., 2014. The coverage and frequency of mass drug administration required to eliminate persistent transmission of soil-transmitted helminths. *Philos. Trans. R. Soc. B* 369 (1645) 20130435.
- Anderson, R.M., Basañez, M.G., 2016. *Mathematical Models for Neglected Tropical Diseases: Essential Tools for Control and Elimination*, vol. 94 Academic Press.
- Aunpromma, S., Tangkawattana, P., Papirom, P., et al., 2012. High prevalence of *Opisthorchis viverrini* infection in reservoir hosts in four districts of Khon Kaen Province, an opisthorchiasis endemic area of Thailand. *Parasitol. Int.* 61 (1), 60–64.
- Boerlage, A.S., Graat, E.A., Verreth, J.A., et al., 2013. Effect of control strategies on the persistence of fish-borne zoonotic trematodes: a modelling approach. *Aquaculture* 408, 106–112.
- Cheng, Q., Jing, Q., Spear, R.C., et al., 2016. Climate and the timing of imported cases as determinants of the dengue outbreak in Guangzhou, 2014: evidence from a mathematical model. *PLoS NTDs* 10 (2), e0004417.
- Echaubard, P., León, T., Suwanatrai, K., et al., 2017. Experimental and modelling investigations of *Opisthorchis viverrini* miracidia transmission over time and across temperatures: implications for control. *Int. J. Parasitol.* 47 (5), 257–270.
- Grundy-Warr, C., Andrews, R.H., Sithithaworn, P., et al., 2012. Raw attitudes, wetland cultures, life-cycles: socio-cultural dynamics relating to *Opisthorchis viverrini* in the Mekong Basin. *Parasitol. Int.* 61 (1), 65–70.
- Hotez, P.J., 2017. Ten failings in global neglected tropical diseases control. *PLoS NTDs* 11 (12), e0005896.
- Jongsuksuntigul, P., Imsomboon, T., 2003. Opisthorchiasis control in Thailand. *Acta Trop.* 88 (3), 229–232.
- Keiser, J., Utzinger, J., 2009. Food-borne trematodiasis. *Clin. Microbiol. Rev.* 22 (3), 466–483.
- Kim, C.S., Echaubard, P., Suwanatrai, A., et al., 2016. Seasonal and spatial environmental influence on *Opisthorchis viverrini* intermediate hosts, abundance, and distribution: insights on transmission dynamics and sustainable control. *PLoS NTDs* 10 (11), e0005121.
- Luby, S.P., Rahman, M., Arnold, B.F., et al., 2018. Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomised controlled trial. *Lancet Glob. Health* 6 (3), e302–e315.
- Michael, E., Gambhir, M., 2010. Transmission models and management of Lymphatic Filariasis elimination. *Adv. Exp. Med. Biol.* 673, 157–171.
- Onsurathum, S., Pinlaor, P., Haonon, O., et al., 2016. Effects of fermentation time and low temperature during the production process of Thai pickled fish (pla-som) on the viability and infectivity of *Opisthorchis viverrini* metacercariae. *Int. J. Food Microbiol.* 218, 1–5.
- Petney, T.N., Andrews, R.H., Saijuntha, W., et al., 2013. The zoonotic, fish-borne liver flukes *Clonorchis sinensis*, *Opisthorchis felinus* and *Opisthorchis viverrini*. *Int. J. Parasitol.* 43 (12), 1031–1046.
- Pinlaor, S., Onsurathum, S., Boonmars, T., et al., 2013. Distribution and abundance of *Opisthorchis viverrini* metacercariae in cyprinid fish in Northeastern Thailand. *Korean J. Parasitol.* 51 (6), 703.
- Sithithaworn, P., Haswell-Elkins, M., 2003. Epidemiology of *Opisthorchis viverrini*. *Acta Trop.* 88 (3), 187–194.
- Sithithaworn, P., Pipitgool, V., Srisawangwong, T., et al., 1997. Seasonal variation of *Opisthorchis viverrini* infection in cyprinoid fish in north-east Thailand: implications for parasite control and food safety. *Bull. World Health Organ.* 75 (2), 125–131.
- Sithithaworn, P., Andrews, R.H., Van De, N., et al., 2012. The current status of opisthorchiasis and clonorchiasis in the Mekong Basin. *Parasitol. Int.* 61 (1), 10–16.
- Sriamporn, S., Pisani, P., Pipitgool, V., et al., 2004. Prevalence of *Opisthorchis viverrini* infection and incidence of cholangiocarcinoma in Khon Kaen, Northeast Thailand. *Trop. Med. Int. Health* 9 (5), 588–594.
- Sripa, B., Bethony, J.M., Sithithaworn, P., et al., 2011. Opisthorchiasis and Opisthorchis-associated cholangiocarcinoma in Thailand and Laos. *Acta Trop.* 120, S158–S168.
- Sripa, B., Brindley, P.J., Mulvenna, J., et al., 2012. The tumorigenic liver fluke *Opisthorchis viverrini*—multiple pathways to cancer. *Trends Parasitol.* 28 (10), 395–407.
- Sripa, B., Tangkawattana, S., Laha, T., et al., 2015. Toward integrated opisthorchiasis control in northeast Thailand: the Lawa project. *Acta Trop.* 141, 361–367.
- Wang, Y.C., Yuen, R., Feng, C.C., et al., 2017. Assessing the role of landscape connectivity on *Opisthorchis viverrini* transmission dynamics. *Parasitol. Int.* 66 (4), 402–412.
- World Health Organization, 2012. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 100B-Biological Agents. A Review of Human Carcinogens*.