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Effect of control strategies on the persistence of fish-borne zoonotic trematodes: A modelling approach

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ABSTRACT

Fish-borne Zoonotic Trematodes (FZTs) are a risk to human health and need to be controlled. A mathematical model was developed to give insight into how and to what extent control strategies change the dynamics of FZTs on integrated agriculture–aquaculture farms. The reproduction ratio R evaluates the effects of control strategies. $R > 1$ implies that the infection may persist, whereas $R < 1$ implies that the infection certainly cannot persist. In the absence of control strategies (default), $R = 1.92$. After implementing control strategies either (i) R and percentages infected hosts in the equilibrium did not change and FZTs persisted (ii) R became smaller, but not below 1, the new equilibrium had lower proportions of infected hosts, and FZTs persisted, or (iii) R became smaller than 1, and all hosts were FZT-free in the new equilibrium. Single chemotherapy of humans, reservoir hosts or both did not change R. Continuous chemotherapeutic treatment reduced R but not below 1 when treating only humans ($R = 1.30$) or only reservoir hosts ($R = 1.69$). A combination could result in $R < 1$, e.g. treating all humans and >54% of reservoir hosts. Snail control could result in $R < 1$ with a decrease in density or increase in mortality of snails. This will occur when either transmission to snails or to fish is <14% of its default value. Stocking fish at >25 g as compared to 0.5 g that is usual in aquaculture practice, or at >14 g in combination with treating all humans, led to $R < 1$. Advantage of using R for evaluating control strategies is that it provides insight into control success or failure even if it would take several decennia to observe this effect in the field.

1. Introduction

Fish-borne zoonotic trematodes (FZTs) occur worldwide and are endemic in most countries in Asia. FZTs consist of liver flukes like *Clonorchis sinensis,* that can lead to cholangiocarcinoma (Chai et al., 2005; Rim, 2005) and intestinal flukes like *Haplorchis pumilio,* that can lead to mild intestinal disturbances in humans (Chai et al., 2005). Definitive hosts of FZTs are humans, pigs or fish eating birds. Adult worms in infected hosts excrete FZT eggs with feces of its host. FZT eggs may be eaten by aquatic snails leading to cercariae. Cercariae are shed into the water, penetrate the skin and the underlying muscle of fish, where they develop into metacercariae. Definitive hosts can become infected by eating raw or undercooked fish (Komiya, 1966). FZTs are associated with aquaculture (Lima dos Santos and Howgate, 2011). Integrated agriculture-aquaculture (IAA) systems may enhance transmission of FZTs, because snails, fish, humans and other vertebrates can be present on a single farm and their manure is often used to fertilize fish ponds (Dung et al., 2010; Sapkota et al., 2008).

To avoid human cases, humans can be prevented from eating raw or improperly cooked fish. However, health education efforts aimed at changing traditional habits have not been very successful (WHO, 2004, 2011). Preventive medication of humans is currently the main control strategy against Opisthorchis and Clonorchis infections (WHO, 2011). It is not easy to obtain insight into the effect of control strategies on the dynamics of FZTs in the different hosts over time, because long-term epidemiological studies are expensive and time consuming. Also, conditions may change during a long-term study and may affect the results, and loss to follow-up is very likely to occur. One powerful tool to obtain more insight is mathematical modelling (De Jong, 1995). Transmission of FZTs between hosts can be modelled and the effects of control strategies can be compared using the reproduction ratio (R) in the situation with and without control strategies. The R is the average number of new cases caused by 1 typical infectious individual in a fully susceptible population (Diekmann et al., 1990). An $R > 1$ implies that the infection could possibly persist in the host populations. An $R < 1$ implies that the infection certainly cannot persist, as the special conditions that lead to exceptions to that general rule do not apply here (Greenhalgh et al., 2000).

Objective of this modelling study was to give insight into how and to what extent control strategies will change the dynamics of FZTs on IAA farms.

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2. Materials and methods

2.1. Model description

The life-cycle of FZTs on IAA farms (Fig. 1) is modeled using Mathematica® 8 (Wolfram, 2011). The model is a deterministic compartmental SI model (Keeling and Rohani, 2008) with the proportion of infected hosts (I) and susceptible hosts (1-I) as variables. Ordinary differential equations (ODEs) describe changes in the proportions infected hosts per day on an IAA farm. The host types are: snails, fish, humans and reservoir hosts (definitive hosts other than humans). The proportions infected hosts increase in time when susceptible hosts become infected and decrease if hosts die or become FZT-free due to control strategies. Snails and fish are assumed to remain infected once infected, as mortality rates of trematodes in snails and fish are low compared to mortality rates of snails and fish (Attwood and Chou, 1978; Boerlage et al., 2013*c;* Chen et al., 1994; Fried et al., 2004; Keiser and Utzinger, 2005; Wright, 1971). Only the host mortality rate of humans is lower than the mortality rates of FZTs (Choi et al., 2004) and thus humans may become disease free.

Density of snails and fish (number per m^2), and total number of humans and reservoir hosts are assumed to be constant. Therefore, we assume that birth rate equals total mortality (natural and parasite dependent) of hosts. Values for all parameters are obtained from literature and used as default values (Table 1). See Appendix A for derivations of the ODEs.

Values of the transmission rates are estimated based on observational studies describing infections of FZTs in hosts on IAA farming systems in Nam Dinh province, Vietnam. In this area, about 13% of *Melanoides tuberculata* snails (Boerlage et al., 2013*a*; Dung et al., 2010), 65% of cultured fish in ponds (Phan et al., 2010), 50% of humans (Dung et al., 2007; Phan et al., 2011) and 61% of reservoir hosts (Lan Anh et al., 2009; average of dogs, cats, and pigs) were infected with FZTs. These percentages are assumed to be at the stable endemic equilibrium, and are used to estimate the default transmission rates to snails, fish, humans and reservoir hosts (Table 1). Relative reduction proportions (p) are used to model how control measures change the transmission rates, i.e. at default transmission rate $p = 1$, and for e.g. 50% reduction in transmission $p = 0.5$. See Appendix B for estimations of the transmission rates and further explanation.

The Next Generation Matrix (NGM) is derived from the ODEs (Diekmann et al., 2010; see Appendix C for explanation and estimations). The NGM enables to calculate the next generation of infected individuals for each infected host type (snail, fish, human and reservoir host) from the infected individuals for each infected host type in the current generation. From the NGM, the dominant eigenvalue ($= R$) and its corresponding eigenvector are derived. The eigenvector is the typical infected individual according to the definition of R. The NGM, R and eigenvector provide insights into if, how and to which extent the different parameters affect the dynamics of FZTs in hosts. A sensitivity analysis of parameter values shows if and how a change in value of 1 parameter affects R if all other values remain at their default value, and whether this can lead to $R < 1$.

2.2. Control strategies

The model with all parameters at the default values (Table 1) is referred to as the default situation (i.e. without control). Control strategies are simulated by changing the value of 1 or more parameter(s) while values of other parameters remain at their default value.

1. Single chemotherapy of either humans, or reservoir hosts or both. After chemotherapy, hosts become FZT-free (Fried et al., 2004) and thus susceptible. In the model, this is incorporated by changing the percentage of infected humans, reservoir hosts or both to 0 at time $t = 0$.
2. Continuous chemotherapy of either humans, or reservoir hosts or both. Contrary to the single chemotherapy, percentages for the treated hosts are kept 0 at all times by starting with 0 infected hosts and additionally changing transmission rates to hosts to 0, because hosts cannot get re-infected.
3. Control of snails, e.g. by poly-culture with snail-eating fish or applying molluscicides, can be a potential control strategy (Hoffman, 1970; Molyneux, 2006; Venable et al., 2000; WHO, 1995). This is modeled by changing the parameters density and mortality of snails.
4. Delayed stocking of fish. Before being stocked in a pond, fish fry are kept under FZT-free conditions (e.g. concrete fish tanks with

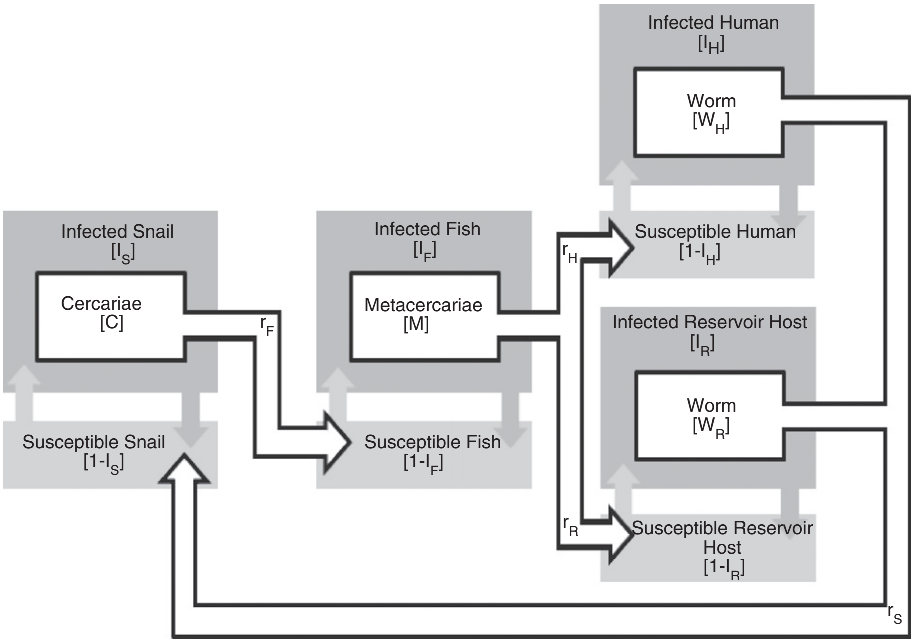

Fig 1. Flowchart of the life-cycle model of FZTs. The host population that consists of infected (I) and susceptible (1-I) hosts are in gray, parasite stages are in white and transmission rates of FZTs to hosts (resp. r_S, r_F, r_H, r_R for snail, fish, human and reservoir host) are indicated in white arrows.