Two different strategies of host manipulation allow parasites to persist in intermediate–definitive host systems

L. J. DE VRIES & F. VAN LANGEVELDE
Resource Ecology Group, Wageningen University, Wageningen, The Netherlands

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Abstract
Trophically transmitted parasites start their development in an intermediate host, before they finish the development in their definitive host when the definitive host preys on the intermediate host. In intermediate–definitive host systems, two strategies of host manipulation have been evolved: increasing the rate of transmission to the definitive host by increasing the chance that the definitive host will prey on the intermediate host, or increasing the lifespan of the parasite in the intermediate host by decreasing the predation chance when the intermediate host is not yet infectious. As the second strategy is less well studied than the first, it is unknown under what conditions each of these strategies is prevailed and evolved. We analysed the effect of both strategies on the presence of parasites in intermediate–definitive host systems with a structured population model. We show that the parasite can increase the parameter space where it can persist in the intermediate–definitive host system using one of these two strategies of host manipulation. We found that when the intermediate host or the definitive host has life-history traits that allow the definitive host to reach large population densities, that is high reproduction rate of the intermediate host or high conversion efficiency of the definitive host (efficiency at which the uninfected definitive host converts caught intermediate hosts into offspring), respectively, evolving manipulation to decrease the predation chance of the intermediate host will be more beneficial than manipulation to increase the predation chance to enhance transmission. Furthermore, manipulation to decrease the predation chance of the intermediate host results in higher population densities of infected intermediate hosts than manipulation that increases the predation chance to enhance transmission. Our study shows that host manipulation in early stages of the parasite development to decrease predation might be a more frequently evolved way of host manipulation than is currently assumed.

Introduction
During the last decades, attention for the effects parasites can have on their hosts has grown, because effects of parasites on the dynamics of the host population can be very large (Price et al., 1986; Minchella & Scott, 1991; Hudson et al., 2002). Consequently, strategies that are evolved, such as how parasites infect their hosts, avoid the immune system and transmit to susceptible hosts, are extensively studied (e.g. Schmid-Hempel, 2011). One way in which parasites influence their host is by manipulating the behaviour, physiology or appearance of their host (Poulin, 2010; Vickery & Poulin, 2010; Schmid-Hempel, 2011). A large number of observations suggest that parasites manipulate the host in their own favour. Often the changes in host behaviour or appearance are subtle, for example changes in the time spent by the host on certain activities (Dianne et al., 2014). However, sometimes the changes can be quite dramatic. For example, the...
parasitic hairworm *Paragordius tricuspidatus* can manipulate its host, the cricket *Nemobius sylvestris*, in a way that the crickets will jump into the water when the hairworms have become adults. This is a new behaviour for the cricket; healthy individuals would not show this behaviour (Sanchez et al., 2008).

Different ways of host manipulation can be distinguished to increase either the survival chances or the transmission rate of the parasites to the next host (Poulin, 2010; Vickery & Poulin, 2010; Schmid-Hempel, 2011). First, parasites can manipulate their host to go to a habitat more suitable for the parasites or the parasite propagules. Second, they can manipulate their host to protect the parasites after they have left the host, for example when they pupate outside the host. Third, in case of vector-bound parasites, they can manipulate their vector in a way that increases the transmission rate of the parasite, for example by making the vector to visit more hosts. Lastly, two ways of host manipulation can be found in trophically transmitted parasites that have both an intermediate host and a definitive host. The parasites start their development in the intermediate host, and after transmission, they finish their development in their definitive host. At the end, the definitive host can infect the uninfected intermediate host again; often eggs are transmitted via the faeces of the definitive host. Transmission from the intermediate host to the definitive host usually implies predation (Lafferty, 1999; Poulin, 2010; Vickery & Poulin, 2010; Dianne et al., 2011). The two strategies of host manipulation in trophically transmitted parasites both involve manipulation of the intermediate host by increasing either the lifespan of the parasite in the intermediate host or the rate of transmission to the definitive host.

The best known strategy is manipulation of the behaviour or appearance of the intermediate host in order to increase the chance that the definitive host will prey on the intermediate host. The transmission rate from the intermediate host to the definitive host will then be increased (Lafferty, 1999; Poulin, 2010; Vickery & Poulin, 2010). A striking example is the colour change of the abdomen of *Cephalotes atratus* ants, the intermediate host, infected with the nematode *Myrmeconema neutropicum*. The abdomens of these ants change during the infection from black to deep red. This will increase the predation risk for the ants by the definitive host of the nematode (Poinar & Yanovik, 2008; Yanovik et al., 2008).

The second strategy, which is less well studied, is manipulation of the intermediate host by the parasite in order to decrease the predation chance (Hammer-schmidt et al., 2009; Dianne et al., 2011; Weinreich et al., 2013). Due to reduction of the predation chance, the lifespan of the parasite in the intermediate host increases to allow for longer growth and development. Only after the parasite completes part of its development, the intermediate host will become infectious to the definitive host (Tierney et al., 1993). During the early developmental stage, it will not be beneficial for the parasites to be consumed by the definitive host or any other predator. Maure et al. (2013) argued that this manipulation to reduce predation risk and therefore the mortality of the immature parasites could be interpreted as ‘bodyguard manipulation’, where manipulated hosts act as bodyguards only during specific phases of the manipulation. They review the diversity of bodyguard manipulation and show that it occurs in several biological systems. For example, when the fresh water amphipod *Gammarus pulex* is infected with the acanthocephalan parasite *Pomphorhynchus laevis*, it shows increased refuge use as long as the infected amphipod is not yet infectious to its fish predators (Dianne et al., 2011). However, research on host manipulation by parasites that decreases the predation chance is limited to date (Maure et al., 2013; Soghiqian et al., 2017). Moreover, it is unknown under what conditions each of these two strategies are prevailed and evolved.

In this study, we use a modelling approach to explore under what conditions the two strategies of host manipulation allow trophically transmitted parasites to persist in predator–prey systems: decreasing predation chance early in the development of the parasite, or increasing predation chance to increase the transmission rate of the parasites. The scope of the study is limited to the possible (ecological) consequences of evolving one strategy or another, where we discuss possible selection pressures that could lead to these strategies. Although we acknowledge that these two strategies are not as separated as they are presented here, decreasing predation chances early in the parasite development may be followed by an increase in predation chances to increase the parasite transmission rate (e.g. Médoc & Beisel, 2011), we explore them separately because there is no reason to believe that they are automatically associated. Especially from an evolutionary point of view, the two strategies often require different or even opposite changes in host behaviour or appearance (Parker et al., 2008). Some modelling studies of manipulative parasites with an intermediate and a definitive host have already been done (e.g. Lafferty, 1992; Fenton & Rands, 2006). Lafferty (1992) created a Lotka–Volterra type of model that investigated the energetic costs of parasites on predators. This model was used as a starting point by Fenton & Rands (2006). Fenton and Rands investigated the effect of host manipulation on the population dynamics of intermediate and definitive hosts. In their model, host manipulation increased predation of infected preys. They concluded that host manipulation could enable parasites to persist in the predator–prey system. Fenton & Rands (2006) assumed in their model that after infection, the intermediate host would directly be infectious to the definitive host and parasites would immediately start to manipulate their intermediate host to increase the
recently infected intermediate hosts. They are the source of infective stages for the definitive host such as mosquitoes. Infection of intermediate hosts occurs as a result of parasitic manipulation. We added manipulation by the parasite to reduce the predation chance during the early developmental stage.

**Model description**

The model of Fenton & Rands (2006) is a density dependent model that has an uninfected intermediate host population \( I_U \), an infected intermediate host population \( I_I \), an uninfected definitive host population \( D_U \) and an infected definitive host population \( D_I \). To model the manipulation by the parasite to reduce the predation chance during the early developmental stage, the development of the parasite was implemented in the model by splitting the intermediate host population into two groups. The first group consists of recently infected intermediate hosts \( I_{I1} \) that contain parasites in an early developmental stage. The second group consists of already longer infected intermediate hosts \( I_{I2} \) that contain parasites in an advanced developmental stage. Host manipulation to allow for the development of the parasite decreases the predation rate on \( I_{I1} \), whereas host manipulation to increase the transmission rate of the parasites increases the predation rate on \( I_{I2} \).

The equations of the model describing the rate of change in population densities of \( I_U, I_I, I_{I1}, I_{I2}, D_U \) and \( D_I \) are as follows (see also Fig. 1 and Table 1):

\[
\frac{dI_U}{dt} = r_U(1 - q(I_U + I_I + I_{I2}))I_U - (\mu + D_U + D_I)I_U - \frac{v\lambda D_U I_U}{\mu} = 1a
\]

\[
\frac{dI_I}{dt} = r_I(1 - q(I_U + I_{I1} + I_{I2}))I_I - (\mu + D_U + D_I)I_I - \frac{v\lambda D_U I_I}{\mu} = 1b
\]

\[
\frac{dI_{I1}}{dt} = (r_{I1}(I_U + I_I + I_{I2}))(I_{I1}) - (\mu + D_U + D_I)I_{I1} - \frac{v\lambda D_U I_{I1}}{\mu} = 1c
\]

\[
\frac{dI_{I2}}{dt} = (r_{I2}(I_U + I_I + I_{I2}))(I_{I2}) - (\mu + D_U + D_I)I_{I2} - \frac{v\lambda D_U I_{I2}}{\mu} = 1d
\]

\[
\frac{dD_U}{dt} = r_D D_U - (\mu + D_U + D_I)D_U = 1e
\]

\[
\frac{dD_I}{dt} = \delta_D I_{I2} D_I - D_I = 1f
\]

The uninfected intermediate host \( I_U \) reproduces following a logistic growth curve as described by the first term of eqn 1a, where \( r_U \) is the growth rate of \( I_U \) at low population density of the total intermediate host population \( (I_{I1} + I_{I2}) \), and \( q = 1/K \), with \( K \) being the carrying capacity for the intermediate host population. Infection of \( I_U \) depends on the transmission rate \( \beta = \frac{v\lambda D_U}{\mu} \), where \( \lambda \) is the rate at which \( D_U \) produces infective stages of the parasite, \( v \) is the rate at which \( I_U \) ingests infective stages of the parasite, and \( \mu \) is the death rate of the infective stages of the parasite outside the hosts. Parasite transmission from the definitive host to the intermediate host often goes through the faeces of the definitive host, which contains infective stages of the parasite (Yanoviak et al., 2008; Dianne et al., 2011). The transmission rate \( \beta = \frac{v\lambda D_U}{\mu} \) reflects the encounters of the uninfected intermediate host with the (faeces of the) definitive host. We assume that the parasite cannot reproduce outside the intermediate or definitive host.

We assume that the infected hosts \( I_{I1}, I_{I2} \) and \( D_I \) do not reproduce, that is the parasite has a strong negative effect on fecundity (Hurd, 1998). The rates at which \( I_U \) and the infected intermediate hosts \( I_{I1} \) and \( I_{I2} \) are preyed on depend on the total definitive host population density \( (D_I + D_U) \) and on the predation rate of the definitive host \( \delta_D \). However, the rate at which the recently infected intermediate host \( I_{I1} \), which contains parasites in an early developmental stage, is preyed on decreases with \( \gamma (0 \leq \gamma \leq 1) \). The parameter \( \gamma \) thus describes the decrease in predation on \( I_{I1} \) due to host manipulation by parasites in an early stage of their development. The rate at which the infected intermediate host \( I_{I2} \), which contains parasites in an advanced developmental stage, is preyed on increases with \( \theta (\theta \geq 1) \). The parameter \( \theta \) describes the increase in predation on \( I_{I2} \) by the definitive host due to host manipulation by parasites to increase the transmission rate. The parameter \( f \) is the rate at which \( I_I \) gets infectious and becomes \( I_{I2} \). The death rate of \( I_{I1} \) is \( \delta_{I1} \), which includes both natural death causes and death due to predation by other predators than the definitive host. Often host manipulation decreases not only predation by the definitive host, but also predation of other predators, for example, due to parasite manipulation of host behaviour that causes the avoidance of risky situations. For the manipulation strategy by parasites in an early stage.
of their development, not only predation by the definitive host but also the death rate $d_{I1}$ due to other predators will decrease with increasing host manipulation $\gamma$ (Lagru et al., 2013). The parameter $m$ describes the fraction of the death rate $d_{I1}$ that involves predation by other predators than the definitive host. With increasing $m$, host manipulation in $I_1$ by the decrease of the predation chance $\gamma$ will result in a lower death rate $d_{I1}$. The death rate of $I_2$ is $d_{I2}$; we assume that $d_{I2}$ is not increased by manipulation of the parasite by $\theta$, as host manipulation that increases predation is most beneficial to the parasite when specifically directed towards the definitive host of the parasite (Parker et al., 2008; Yanoviak et al., 2008; Lagru et al., 2013). Even if increasing nonhost predation is an unavoidable side effect, we assume that this manipulation may nonetheless yield a net benefit to the parasite, at least up to a point, and hence, we left an effect of $\theta$ on predation by nonhost predators out of the model as it would not change the results qualitatively.

The reproduction of the uninfected definitive host $D_U$ depends on the intermediate hosts caught by $D_U$, which is determined by the total intermediate host population densities ($I_U$, $I_{I1}$ and $I_{I2}$), and on the predation rate. The predation rate is determined by $\delta_U$, $\gamma$ and $\theta$. The parameter $e$ describes the conversion efficiency, which is the efficiency at which $D_U$ converts the caught intermediate hosts into offspring. Infection of $D_U$ depends on the infected intermediate host $I_{I2}$ caught by $D_U$. The caught $I_{I2}$ depends on the predation rate $\delta_U$ and the increased predation on $I_{I2}$ due to host manipulation $\theta$. The death rate of $D_U$ is $d_{D_U}$, whereas the death rate of $D_I$ is $d_{D_I}$.

### Table 1 Symbols, description of the parameters of the model and their default values.

| Parameter | Description [and units] | Parameter value |
|-----------|--------------------------|-----------------|
| $I_U$     | Uninfected intermediate host population density [number of individuals per unit area] | 0–10 |
| $I_{I1}$  | Recently infected intermediate host population density [number of individuals per unit area] | 0–10 |
| $I_{I2}$  | Longer infected intermediate host population density [number of individuals per unit area] | 0–10 |
| $D_U$     | Uninfected definitive host population density [number of individuals per unit area] | 0–10 |
| $D_I$     | Infected definitive host population density [number of individuals per unit area] | 0–10 |
| $r_1$     | Reproduction rate of intermediate host [1/unit of time] | 0.03 |
| $e$       | Conversion efficiency of definitive host [–] | 0–1 |
| $q$       | $1/K$ [1/number of individuals per unit area], with $K$ being carrying capacity [number of individuals per unit area] | 0.1 |
| $\delta_U$ | Predation rate of definitive host [1/(unit of time $\times$ number of individuals per unit area)] | 0.005 |
| $\beta$   | $\frac{1}{K}$, transmission rate from definitive to intermediate host [1/(unit of time $\times$ number of individuals per unit area)] | 0.027 |
| $\lambda$ | Rate of production of infective stages of parasite [1/(unit of time $\times$ number of individuals per unit area)] | 54 |
| $\nu$     | Rate at which $I_1$ ingests infective stages of the parasite [1/unit of time] | 0.0001 |
| $\delta_{I1}$ | Death rate of infective stages of parasite outside hosts [1/unit of time] | 0.2 |
| $\gamma$  | Decrease in predation on recently infected intermediate hosts [–] | 0–1 |
| $\theta$  | Increase in predation on longer infected intermediate hosts [–] | 1–10 |
| $f$       | Rate at which $I_1$ gets infectious and becomes $I_2$ [1/unit of time] | 0.005 |
| $m$       | Fraction of the death rate $d_{I1}$ that involves predation by other predators than the definitive host [–] | 0.5 |
| $d_{I1}$  | Death rate of recently infected intermediate hosts [1/unit of time] | 0.01 |
| $d_{I2}$  | Death rate of longer infected intermediate hosts [1/unit of time] | 0.01 |
| $d_{D_U}$ | Death rate of uninfected definitive hosts [1/unit of time] | 0.01 |
| $d_{D_I}$ | Death rate of infected definitive hosts [1/unit of time] | 0.02 |

### Model analysis

**Effects of two strategies of host manipulation on parasite persistence**

To analyse the model behaviour, the equilibria were determined first. Then, the effect of predation increase $\theta$ and predation decrease $\gamma$ on the model behaviour and model outcomes was analysed, followed by the analysis of several other parameters. We could determine the first three model equilibria analytically where the parasite is absent. These model equilibria were equivalent to the model equilibria determined by Fenton and Rands (Table 2). The first equilibrium of the model with all population densities being 0 is an unstable equilibrium. The second equilibrium allows only $I_U$ to stably persist in the system at carrying capacity when $K < \frac{4\nu}{\beta e}$, whereas population densities of $I_{I1}$, $I_{I2}$, $D_U$ and $D_I$ are all larger than 0. The third equilibrium with both $I_U$ and $D_U$ larger than 0 is stable when $K > \frac{4\nu}{\beta e}$ and $\theta < F1$ or $\gamma > F2$ (Table 2). The population density of $I_{I2}$ is $\frac{K}{0.5\nu}$ and the population density of $D_U$ is $\frac{4\nu + \beta e}{3\nu}$. The population densities of $I_{I1}$, $I_{I2}$ and $D_I$ are 0. In these three equilibria, the parasite cannot invade. The fourth equilibrium with the parasite being present in the system could not be determined analytically. The numerical model analyses show that population densities of $I_{I1}$, $I_{I2}$, $D_U$ and $D_I$ are all larger than 0. The fourth equilibrium of our model differs from the fourth equilibrium of the model of Fenton and Rands, due to the distinction that we made between $I_1$ and $I_2$. The fourth equilibrium of our study is stable when $K > \frac{4\nu}{\beta e}$ and $\theta < F1$ or $\gamma > F2$. 

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The equations for the population densities of the third equilibrium could not be determined. The requirements for the equilibria 0-3, 0-1 and 0-2 to be stable are given as well. For equilibrium 3, we found stable values as well as oscillations.

A more detailed description of the calculation of the model equilibria and stability requirements can be found in Appendix A.

The parameter regions in which the different equilibria can be found are shown in Fig. 2. Region 1 in Fig. 2 corresponds with equilibrium 1 of Table 2, region 2 with equilibrium 2 and region 3 with equilibrium 3. In region 4, the host populations are oscillating over time. It can be observed that with an increasing degree of host manipulation, which means either a higher value of \( \theta \) or a lower value of \( \gamma \), the parasite is more likely to persist in the system, that is regions 3 and 4 together cover a larger part of the parameter space. The effect of manipulation of \( I_2 \) by \( \theta \) on the model behaviour as shown in Fig. 2a is similar to the effect observed by Fenton and Rands. Here, at high degree of host manipulation in \( I_2 \), which means at high values of manipulation of \( I_2 \) by \( \theta \), the host populations start to show oscillating behaviour, like Fenton and Rands found. However, host manipulation in \( I_1 \) by decreasing \( \gamma \) seems to involve lower risks of host population oscillation (Fig. 2a–f). When \( \theta = 1 \), even no oscillation of host populations with decreasing \( \gamma \) is observed (Fig. 2d). Oscillation of the populations increases the risk that one of the populations would go extinct, and this would also cause the extinction of the parasite. When the predation effect decreases for lower values for \( \theta \), the oscillations are less likely to occur as the predator population reacts less strongly to changes in the prey population, leading to a stable equilibrium. Also, decreasing value of \( \delta_1 \) leads to a smaller parameter space that the populations oscillate (not shown).

Another difference in model behaviour can be observed when comparing manipulation in \( I_1 \) with manipulation in \( I_2 \). For systems with a definitive host with a high conversion efficiency \( \epsilon \), manipulation in \( I_1 \) increases the parameter space in which the parasite can persist a lot more than manipulation in \( I_2 \) (Fig. 2g–i).

**Effects of other parameters on parasite persistence**

When comparing Fig. 3a, b with 3c, d, the effect of increasing the rate \( f \) at which \( I_1 \) gets infectious and becomes \( I_2 \) can be observed. When this rate \( f \) is increased, that is shorten the development time of the parasite in the intermediate host, the parameter space where the parasite can persist increases due to manipulation of \( I_1 \) by decreasing predation \( \gamma \) or \( I_2 \) by increasing predation \( \theta \) (Fig. 3c, d).

Second, reducing the reproduction rate \( r_1 \) of the uninfected intermediate host \( I_1 \) decreases the effect that manipulating \( I_1 \) by \( \gamma \) has on the parameter space for parasite persistence, whereas the effect of manipulation of \( I_2 \) by \( \theta \) increases, because manipulating \( I_2 \) is then also beneficial for definitive hosts with slightly higher conversion efficiencies (Fig. 3e, f). So the reproduction rate influences the parasite under a broader range of conditions to manipulate either \( I_1 \) or \( I_2 \). At higher reproduction rates of the intermediate host, the parasite can occur under a broader range of conditions when manipulating \( I_1 \) by \( \gamma \), whereas at lower reproduction rates it is more beneficial to manipulate \( I_2 \) by \( \theta \).

The conversion efficiency \( \epsilon \) has a comparable effect as the reproduction rate \( r_2 \). At higher values of \( \epsilon \), the parameter space for parasite persistence is larger due to manipulation of \( I_1 \) by \( \gamma \) (Fig. 3a, b). Both the effect of the
reproduction rate $r_I$ and the effect of the conversion efficiency $e$ can be explained by the influence they have on the uninfected definitive host population density $D_U$. Population density of $D_U$ increases with increasing $r_I$ or $e$. At higher population density of $D_U$, the predation of the intermediate hosts will increase. Because of this high predation pressure, decreasing the predation in the early developmental stage of the parasite $\gamma$ will result in broader conditions for parasite persistence compared to increasing the predation later in its development $\theta$.

Figure 3g, h shows that a decrease in the transmission rate $\beta$, for example by a decrease in the production of infective stages $\lambda$ in the infected definitive host $D_I$, will decrease the parameter space where a parasite can invade the system. This can be explained by a decrease in the parasite load in the system with a decrease in production of infective stages. Increasing the death rate $d_{II}$ of $D_I$ has a similar effect as decreasing $\beta$ (Appendix B). So it will be beneficial for conditions of parasite persistence to increase the production of infective stages and to decrease its lethality to its definitive host, which suggests that the parasite increases its transmission $\beta$ together with reduction of its damage of the definitive host (i.e. virulence).

Figure 3i, j shows that an increase in the mortality of infected intermediate hosts $d_{Ii1}$ and $d_{Ii2}$ decreases the conditions for parasite persistence in the system. Also, no oscillation is found anymore with manipulation of $I_{i2}$ (Fig. 3i). The decrease in parameter space in which the parasite can persist can be explained by the dependence of the parasite on the survival of its intermediate host. It is not beneficial to the parasite to increase the mortality of its host before it is transmitted.

Figure 3l shows that the conditions for parasite persistence with manipulation of $I_{i1}$ by $\gamma$ decrease slightly with decreasing value of $m$, the fraction of the death rate $d_{II}$ that involves predation by other predators than the definitive host. This means that the range of influence of $\gamma$ is larger when $\gamma$ also decreases predation from other predators than the definitive host. The parameter
space where the parasite can persist increases when the parasite targets not only its definitive host when decreasing predation, but also decreases predation by other predators. However, when manipulating $I_{12}$ by $\theta$, no effect of $m$ is observed (Fig. 3k), as $m$ only increases the effect of manipulation in $I_{11}$.

Consequences for population densities

The density of $I_{11}$ increases with an increase in host manipulation of $I_{11}$ by $\gamma$ (Fig. 4a). This increase can be explained by the decrease in predation pressure due to the decrease in total definitive host population density ($D_{11} + D_{12}$) (Fig. 4d, c). An increase in manipulation of $I_{11}$ by decreasing predation $\gamma$ (Fig. 4a–e) results obviously in an increase in the density of $I_{11}$ as manipulation reduces its predation. The consequences are an increase in $I_{12}$ and therefore an increase in the density of infected definitive hosts $D_{1}$. This increased infection causes a decrease in the density of uninfected predators $D_{10}$. However, with even higher degree of manipulation of $I_{11}$ by $\gamma$, the density of infected predators $D_{1}$ decreases. This decrease can be explained by the decrease in population density of $D_{10}$ decreasing the amount of definitive hosts that can get infected (Fig. 4d).

This negative effect on population density of $D_{1}$ outweighs the effect of the increase in the density of infected prey on population density of $D_{1}$ at this point, as can be observed in Fig. 4f (plotting $I_{12} \times D_{1}$ helps to illustrate how $I_{12}$ and $D_{1}$ together affect population density of $D_{1}$).

The density of $I_{11}$ increases with an increase in host manipulation of $I_{12}$ by $\theta$ (Fig. 4g). This increase can be explained by the decrease in total predation pressure, due to the decrease in the total definitive host population density ($D_{11} + D_{12}$) (Fig. 4j, k). The increase in manipulation of $I_{12}$ by $\theta$ results first in an increase in $I_{11}$, $I_{12}$ and $D_{1}$, and then in a decrease with further
increase in $\theta$ (Fig. 4h, i, k). First, host manipulation that increases predation by $\theta$ facilitates the presence of the parasite in the system, which causes infected host population densities to increase. Later, the high degree of host manipulation in $I_{12}$ by $\theta$ leads to a high removal rate of $I_{12}$, leading to a decline in population densities of $I_{11}$, $I_{12}$ and $D_U$ and at a certain point also to oscillation of the populations. With increasing manipulation of $I_{12}$ by $\theta$, the population density of $D_{12}$ decreases. The first steep decrease in $D_U$ can be explained by the increase in $I_{12}$. The later decrease in $D_U$, when $I_{12}$ is decreasing due to predation, can be explained by the transfer of $D_U$ to $D_I$ when preying more and more on the infected intermediate host $I_{12}$ with the increasing degree of manipulation by $\theta$.

We found for all our results that changing the values of the parameters did not lead to changes in the qualitative behaviour of the model.

**Discussion**

Parasites are able to manipulate their hosts in different ways, often by increasing their transmission rate or survival (Poulin, 2010; Schmid-Hempel, 2011). In the intermediate–definitive host system as investigated in this paper, increasing the transmission rate by increasing predation by the definitive host is the most well-known way trophically transmitted parasites manipulate their host (Poulin, 2010). Relatively few researches have been performed to date on host manipulation by parasites that decrease the predation early in their development (Maure et al., 2013; Soghigian et al., 2017). This could indicate that parasites have evolved this strategy infrequently. However, behaviour that decreases predation, like decreased activity and increased sheltering, is in most cases more difficult to measure than behaviour that increases predation.
(Parker et al., 2008; Dianne et al., 2014). As prey usually try to avoid being predated on, predation avoidance behaviour will easily be overlooked when studying host manipulation. Another reason why this predation suppression is rarely observed was postulated by Parker et al. (2008): suppression may be more costly to the parasite. The model outcomes of this study suggest that manipulation in the early developmental stage of the parasite can be as beneficial to the parasite as manipulation later in the development, in terms of the conditions where the parasite can persist in the system. Moreover, manipulation to decrease the predation chance of the intermediate host results in higher population densities of infected intermediate hosts (l01 and l02) than manipulation that increases the predation chance to enhance transmission (see Fig. 4).

Another advantage of manipulating to decrease host predation in the early developmental stage is that the risk of destabilizing the host populations by oscillations is low, whereas host manipulation later in the development to increase predation involves higher risks of destabilization of the host populations (Fenton & Rands, 2006). Furthermore, Parker et al. (2008) argued that host manipulation by parasites that decreases predation early in the development of the parasite evolves more easily in an intermediate–definitive host system than manipulation increasing their transmission rate does, as manipulation in the early stage to decrease predation is less limited to a specific predator. It is beneficial to the parasite to decrease predation in general during this stage (Lagrou et al., 2013), whereas later in its development it is beneficial to the parasite to direct its manipulation specifically towards its definitive host (such as in the example of the colour change of the abdomen of C. atratus ants, Yanoviak et al., 2008). This is more costly to the parasite.

Although we indicated some advantages of host manipulation early in the development of the parasite to decrease predation, more factors influence the effect of the two manipulation strategies of the parasite on the conditions for its persistence. For example, the definitive host can act as selection pressure for either of these strategies, depending on its population density. When the intermediate host or the definitive host have life-history traits that allow the definitive host to reach large population densities, that is high reproduction rate of the intermediate host or high conversion efficiency of the definitive host, respectively, evolving manipulation to decrease predation in the early developmental stage of the parasite will be more beneficial for the conditions of parasite persistence than to increase predation later in its development. We show that in a system with a large definitive host population density, which puts a large predation pressure on the intermediate host, decreasing the predation early in its development results in a larger parameter space for persistence of the parasite than increasing predation later in its development. Also, our study suggests that when the definitive host population density is small and transmission possibilities are more limiting to the parasite, it is beneficial to increase the predation later in its development (see also Vervaekte et al., 2006). Other drivers for population density of the definitive host, such as availability of alternative prey and the absence of competing predator species (Hassell & Comins, 1976), will have a similar effect on the benefits of the two strategies of host manipulation. We should take into account that in our model, the definitive host controls the population density of the intermediate host due to strong top-down effects, so an increase in reproduction rate of the intermediate host results in an increase in the population density of the definitive host (cf. Oksanen et al., 1981). However, in natural systems, an increase in reproduction rate of the intermediate host could result in an increase in the population density of the intermediate host with weak or absent top-down control. Then, a reverse effect on the benefits of the two strategies could be expected.

Manipulating the intermediate host to decrease predation early in the development of the parasite becomes more effective when alternative predator species are present, which could change the relative advantage of the two manipulation strategies. When many nonhost predators predate on the intermediate host, we found that it is more beneficial to decrease the predation early in the development of the parasite. This can, for example, be observed for the parasitic acanthocephalan worm P. laevis, which uses a couple of fish species as its definitive host, whereas many other fish species prey on its intermediate host G. pulex (Hine & Kennedy, 1974). Then predation risk early in the development of the parasite is high. Our model predicts that manipulation early in the development to decrease predation would be most beneficial to this parasite. Pomphorhynchus laevis was indeed found to manipulate its intermediate host early in its development to decrease the predation (Dianne et al., 2014).

Parasites can have large effects on species abundance and interactions in food webs (Lafferty et al., 2008). Often the focus is on the negative impacts parasites have on their host populations (Winterntitz et al., 2012; Granovitch & Maximovich, 2013). However, our study predicts that parasite manipulation, resulting in either predation decrease γ or increase θ of the intermediate host by the definitive host, can have a positive effect on the intermediate host population density. This is counterintuitive considering the negative effect of the parasite on the fertility of the intermediate host. However, the positive effect can be explained by the negative impact of the parasite on the definitive host population, which leads to decreasing predation pressure on the intermediate host and increases in this way the intermediate host population density.

Parameterization of the model could provide more insight in the expected frequency at which both strategies of host manipulation will be used by parasites in natural systems, especially the reproduction rate of the intermediate host and the conversion efficiency of the
definitive host are relevant for the effect of the two strategies. There is a need for more data on natural systems showing manipulation to decrease predation in the intermediate host. Our model could help to determine in what systems this manipulation strategy can be found, for example when the definitive host population is relatively large or in systems with a relatively high nonhost predator species richness. Some experimental studies have shown parasites use the strategy manipulation to decrease predation in the intermediate host (Hammerschmidt et al., 2009; Weinreich et al., 2013; Dianne et al., 2014), but no field data on this subject were found.

The lack of compelling evidence for host manipulation has prompted some critical reviews (Poulin et al., 1994; Poulin, 2000, 2010; Thomas et al., 2005; Lefèvre & Thomas, 2008). Although few studies report about host manipulation in early stages of the parasite development to decrease predation, our study provides testable hypotheses to investigate possible examples in more detail. Moreover, our study contributes to understanding under what conditions the two studied strategies are prevailed. It suggests that manipulation in early stages of the parasite development to decrease predation might be a more frequently evolved host manipulation strategy than is currently assumed, as the conditions in which the parasite can persist in predator–prey systems as well as population densities of infected intermediate hosts increase with higher degree of manipulation. Finally, our study indicates that life-history and ecological variables may have played an important role in the evolution of manipulation of host behaviour by parasites in intermediate–definitive host systems.

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Conflict of interest

The authors declare no conflict of interests.

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not be solved. The equilibria that could be determined were as follows:

| Equilibria | I_U | I_1 | I_2 | D_U | D_i |
|------------|-----|-----|-----|-----|-----|
| 0          | 0   | 0   | 0   | 0   | 0   |
| 1          | K   | 0   | 0   | 0   | 0   |
| 2          | 0   | 0   | 0   | r_1 (d_{0u} - d_{0i}) / d_{0u} | 0   |

Stability of equilibria 0, 1 and 2 could be determined by solving the Jacobian of the system in the absence of the parasite, so with only I_U and D_U populations at equilibrium 2.

\[ J_{\text{predator-prey}} = \begin{bmatrix} r_1 - 2 r_1 q I_U & -\delta_U I_U \\ -\delta_U D_U & -\delta_U I_U \end{bmatrix} \]

The determinant and trace of this Jacobian for equilibrium 2 were determined:

\[ \text{Determinant} = d_{0u} r_1 - \frac{r_1 d_{0u}^2 q}{\delta_U \varepsilon} \]
\[ \text{Trace} = -\frac{d_{0u} q r_1}{\delta_U \varepsilon} \]

Equilibrium 2 is stable when the trace of the Jacobian is smaller than 0 and the determinant of the Jacobian is larger than 0. The trace of the Jacobian is always smaller than 0. However, the determinant will only be larger than 0 when \( K > \frac{d_{0u}}{d_{0i}} \) (note that \( K = 1/q \)). This leads to the requirement \( K > \frac{d_{0u}}{d_{0i}} \) for equilibrium 2 to be stable, whereas equilibrium 1 will be stable when \( K < \frac{d_{0u}}{d_{0i}} \). Equilibrium 0 is unstable (Table 2).

The fourth equilibrium could not be determined analytically. However, the requirements for this equilibrium to be stable could be determined with the Jacobian of the full model. This was done with the same approach Fenton \\& Rands (2006) used. To do this, the first Jacobian of the full model at equilibrium 2 was determined based on I_U, D_U, I_1, I_2 and D_i.
The requirement for the predator–prey system to be stable should also still be fulfilled for the equilibrium with presence of the parasite to be stable, $K > \frac{d_{hi}}{\delta_{hi}e}$. However, equilibrium 2 should be unstable to enable the parasite to invade. The stability of equilibrium 2 is determined not only by the upper left part of the Jacobian, but also by the lower right part:

$$
\begin{vmatrix}
-D_U \gamma \delta_U - f & 0 & \beta D_U \\
-d_{hi}(\gamma m + (1 - m)) & -\theta \delta_U D_U - d_{h2} & 0 \\
0 & \delta_U \theta D_U & -d_{hi}
\end{vmatrix}
$$

Equilibrium 2 is unstable when the determinant of the lower right part of the Jacobian is smaller than 0 and the trace of the lower right part of the Jacobian is larger than 0.

\[
\text{Determinant} = \frac{1}{\delta_{hi}^2 e^2} \left( \beta d_{Du} f r_1 \theta (\delta_{hi} e - d_{Du} q) ight) - d_{hi} (d_{hi} \delta_{hi} e (1 + m (\gamma - 1)) - d_{hi} \gamma q r_1 + \delta_{hi} e (f + \gamma r_1)) (d_{hi} \delta_{hi} e + r_1 \theta (\delta_{hi} e - d_{Du} q)))
\]

\[
\text{Trace} = d_{hi} (m - 1 - \gamma m) - d_{hi} - f - \gamma r_1 - r_1 \theta + \frac{d_{Du} \gamma q r_1}{\delta_{hi} e} + \frac{d_{Du} q r_1 \theta}{\delta_{hi} e}
\]

From this criterion, it can be derived that the parasite is able to invade in the system when

\[
\theta > -\frac{d_{hi} d_{Du} \delta_{hi} e (\delta_{hi} e (d_{hi} + f + d_{hi} m (\gamma - 1)) + \gamma r_1 (\delta_{hi} e - d_{Du} q))}{\gamma (\delta_{hi} e - d_{Du} q) (-\beta d_{Du} f + d_{Du} \delta_{hi} e (d_{hi} + f + d_{hi} m (\gamma - 1)) + d_{hi} \gamma r_1 (\delta_{hi} e - d_{Du} q))}
\]

or

\[
\gamma < -\frac{d_{hi} d_{Du} \delta_{hi} e^2 (d_{hi} m - d_{hi} - f) + r_1 \theta (\beta d_{Du} f + d_{Du} \delta_{hi} e (d_{hi} m - d_{hi} - f)) (\delta_{hi} e - d_{Du} q))}{d_{hi} (d_{hi} \delta_{hi} e m + d_{hi} e r_1 - d_{Du} q r_1) (d_{hi} \delta_{hi} e + r_1 \theta (\delta_{hi} e - d_{Du} q)))}
\]

**Appendix B**

Effect of the death rate of infected definitive hosts $d_{hi}$ on the model behaviour for (a) $\theta$ and (b) $\gamma$. The regions are similar as in Fig. 2. Comparison between Fig. 3a, b shows the effect of increasing $d_{hi}$ on the model behaviour. Similar parameter values are used except for $d_{hi}$ of which the value was increased compared to its value in Fig. 3a, b. See Fig. 2 for explanation of the different regions in the graphs. The parameter values used for the graphs are as follows: $d_{hi} = 0.03$, $r_1 = 0.03$, $q = 0.1$, $\delta_{hi} = 0.005$, $\nu = 0.0001$, $\lambda = 54$, $\mu = 0.2$, $f = 0.005$, $m = 0.5$, $d_{hi} = 0.01$, $d_{h2} = 0.01$, $d_{Du} = 0.01$, $\gamma = 1$ (a) and $\theta = 1$ (b).