We thank the reviewer for their positive evaluation and the constructive comments. We would like to respond to the comments point by point in the blue text below.

This is an interesting contribution that is worthy of consideration for publication. Many parasites engage in host manipulation to facilitate transmission to predators that serve as terminal hosts. This manipulation can increase parasite fitness in the short-term, but destabilizing predator-prey dynamics in the long run. The question at hand in this paper is, how does coinfection alter this past conclusion? This is a valuable question, and I think the paper does present a compelling answer (which is, it's complicated, but coinfecting manipulation can rescue parasitism in some situations).

The previous reviewer had concerns about model clarity, and noted that they were not qualified to evaluate the mathematical details. Not having seen the previous version, it is hard for me to comment on whether clarity has improved appreciably. I do think that there remains room for further improvement, but I think overall the paper is close to acceptable. Below I provide a range of minor comments. However, in addition to my comments I would urge the Editor to seek the opinion of a mathematical biologist (which I am not) who could better evaluate the formulation and analysis of the model. I would also suggest that the authors should make their Mathematica notebooks and any code used to obtain solutions or build figures, publicly available on Dryad or Figshare or Zenodo, or an equivalent repository.

We have the Mathematica notebooks, also converted to PDF available on GitHub link that will be publicly available once the manuscript is accepted. The figures are generated directly from the code and will also be embedded in the Mathematica and the ensuing pdfs.

Broad comments:

The current model formulation is focused on situations where host manipulation (beta) increases predation rate, facilitating transmission. In this focus the authors emphasize beta >= 0. However, the term beta could be even more generically applicable: when beta is negative, it can represent effects of infection that reduce predation risk. For instance if parasites suppress risk-taking to avoid premature consumption, or if parasites induce sickness behaviors in their hosts that reduce mobility and foraging activities that might expose them to predation. Thus, there is an opportunity to use the present model to consider both predation facilitation and predation suppression in one context.

We agree with the reviewer that, in nature, host manipulation is not limited to enhancing the predation rate and can also be suppression to avoid non-host predation and/or host predation when the parasite is not yet ready to transmit (Hafer and Milinski 2015). The effect of suppression was explored in one theoretical paper (Iritani and Sato 2018). However, in the formulation of our model, reducing host manipulation is not at all beneficial for the parasites. In particular, it only reduces transmission from intermediate hosts to definitive hosts and, therefore, does not guarantee the completion of the parasite's life cycle. Specifically, we show that in Figure 5, if beta_w is smaller than a threshold, the parasite population goes extinct because its basic reproduction R0 is smaller than 1.

To study suppression in host manipulation, it requires incorporating some benefits to the suppression, such as including a non-host predator that serves as a dead end for the parasite or add a parasitic state that is not ready to transmit. If we also incorporate multiple infections as we do in the current model, we will make the model much more complicated to analyse. We needed to simplify these aspects because we

would like to focus on the effect of multiple infections in this manuscript. We discuss this issue in in line 335-345.

The paper spends a great deal of time discussing bistability and when it happens, or not. If the authors wish to be read, and their work understood, by a broader audience, they may need to clearly define what they mean by this , and provide an illustrative example. This leads me to a still broader point, that Reviewer 1 noted that the figures are often not very approachable for a non-specialist reader, and I found that to still be true. I did not fully understand all the figures despite some work at it. Fig 3 was quite good. Figure 4 took some digesting – make it easier to see that the vertical lines in A) correspond to (B) and (C), explicitly say so in the legend. Use words to define axes (e.g., fww/fw is obscure, text can make it intuitive). You could do more to show where bistability is in panel C, for readers who do not inherently understand these kinds of figures (e.g., grey shading between r8 and 39.9 to match the grey bistability in panel A. Maybe show some plots of I_s and I)_w through time to illustrate different outcomes in (C). Figures 5 and 6 I found challenging. What are the different shading densities in B? Why does Bistability vs single equilibrium matter (panel A)? Whose extinction are we talking about in A and B – the host, the predator, the parasite, all of the above?

We thank the reviewer for the comments on improving the manuscript for broad readers. Indeed, the occurrence of bistability is an important result of our model. We attempt to explain it more in lines 236-241. We also added a panel with population dynamics in Figure 5, as suggested.

We completely agree that the figures will require quite some time to comprehend as this is a rather complicated model, and we would like to convey information but also do not want to make a figure with too many panels. Following the reviewer's suggestions, we modify Figure 2, 4, 5 and 6. We hope that this modification make it easier for readers to understand.

Minor comments:
Line 2: "parasites with complex life cycleS"

This has been fixed

Line 54: which parasite wins?

We clarified which parasite wins in line 52-53

Line 63: parasitism that increases the natural death rate of the first host also can alter the entire predator-prey dynamic (prey's natural death rate does enter into the equilibria and stability of predator-prey dynamics)

We agree with the reviewer that increasing the natural death rate of the intermediate host can alter the predator-prey dynamics. However, we believe it will not be as strong as the increase in predation rate because dead infected intermediate hosts do not become food for definitive hosts. Nevertheless, we modified the phrase in line 60-61 because to understand exactly the difference in the effect on ecological dynamics between natural death and death by predation, we need to conduct a thorough analysis regarding the two parameters, which is not our focal in this manuscript.

Figure 1: It's a nice picture (photo credit?), and an interesting system. But there's a lot of detail here that isn't necessary, and its not clear that this figure is really

necessary to the scientific point of the paper, making it feel like it takes excess space. Also, if retained then please provide a citation for the "shown by Martin Kalbe".

We have reduced the details of the system shown in the photograph. The photograph captures the essence of the problem that we are tackling by showing the numerosity of parasites that can inhabit a single host all vying for control. The photograph was taken by Martin Kalbe and is meant as a post-humous (https://www.evolbio.mpg.de/3245109/martinkalbe) acknowledgement to his encouragement for supporting the ideas in this manuscript.

Line 96: one or double but not multiple infections: What does this assumption mean biologically, how realistic is it empirically? Isn't a Poisson or negative binomial distribution more typical, where coinfected individuals are often heavily co-infected? I'm not saying this must be changed, but at least comment on its realism or lack thereof empirically.

Indeed, this is an important simplification of our model. As the reviewer pointed out, the distribution of parasites in host is typically negative binomial distribution (Wilson et al. 1996 Functional Ecology). However, incorporating this in our model would make it very complicated and impossible to have analytical exploration. Instead we aim to focus on a simpler case first as our focus is on co-transmission. We add a clarification about this simplification in line 101-107

Line 102: Do we care about whether the final host is singly infected vs multiply? E.g., can the parasites reproduce asexually or do they benefit from ensuring a mating partner gets into the final host with them? (note, it became clear later, with fw vs fww that this might matter)

At this stage in the manuscript, we explain the dynamics of transmission and, indeed, do not mention the impact of the presence/absence of another parasite in the final host. This allows for the base model to be agnostic of any assumption on the fitnesses at this stage. In our model, the difference between singly and doubly infected definitive hosts lies in the reproduction rate of the parasites (f_w for single infection and f_{ww} for double infections). If $f_w < f_{ww}$, then it means that a single infection results in fewer parasites than a double infection, which suggests that co-infecting parasites cooperate and boost reproduction. The contrasting situation, $f_w > f_{ww}$ can be the case if parasites have to compete for resources inside the host. We explored how this difference affects the ecological dynamics of the system in Figure 6.

Regarding sexual reproduction in the definitive hosts, we acknowledge that this is common in many parasitic systems. However, since it requires taking into account different types of parasites (e.g. male vs female), this again makes our model unwieldy for analysis.

The rationale of the term q (lines 103-104) is obscure – why not omit this, it adds a term unnecessarily and could just be dropped. If you retain it, what's the biological basis? Is this just random or is there some phenotypic basis? is it meant to be random which, or are there priority effects (first versus second infection, older vs younger, larger vs smaller), or genotypic effects?

The term q is the probability that two parasites infect the definitive host when susceptible definitive hosts consume doubly infected intermediate hosts. In the scope of our model, we do not specify the underlying mechanism, but it could either by chance, i.e. when two parasites are inside the definitive hosts, only one can make it, or it could have some phenotypic basis of the host, that is, host's immune system is strong such that only one parasite survives when infection happens.

We showed that the term q does have an important impact on the ecological dynamics, such that the bigger the value of q, the less likely the system exhibits bistability (Figure 6B). When q = 1, there is no room for bistability, suggesting that parasite's persistence is guaranteed. We discuss this aspect in line 346-357.

Line 105: "when hosts encounter parasites": which host? Intermediate or final? This section is garbled and unclear, seems to bounce between ideas, needs streamlining

We mean both host species, and we specified it in line 112-114 as suggested. In particular, we assume that once intermediate hosts encounter the parasite pool and when definitive hosts consume infected intermediate hosts, parasites will always manage to get into the definitive and intermediate hosts.

This is a common assumption in many theoretical work in host-parasite system. We could add another parameter representing the probability of infection once the host meet with the parasite. However, this is not our focus in this manuscript. In addition, the current model is complicated enough with 17 parameters, therefore, we reduce the use of unnecessary parameters.

Equation 1: from the outset I worried at the absence of a carrying capacity for the prey, later it became clear that the R(I_total) term could be altered to accommodate density dependence. The authors note that the linear reproduction is both unrealistic and destabilizing, so I suggest omitting the linear reproduction compoment in the model and results, and just going straight to the density dependent formulation at the outset – more succinct, more realistic.

We are hesitant to discard the linear birth function by deeming it unrealistic, as in reality, deriving the exact form of the birth function for the prey can be extremely challenging. The important aspect that we discuss is the instability of the population dynamics. In nature, we do have cyclic dynamics for predator and prey. However, as mentioned in the manuscript, analyzing the invasion possibility of parasites in cyclic predator-prey dynamics requires a different technique, which is beyond the scope of the current manuscript. Moreover, we showed that, in cyclic dynamics, although the basic reproduction ratio R0 > 1 suggests the spread of parasites, the parasites eventually cannot invade and persist. We, however, agree with the reviewer that for the sake of succinctness, we reduce the focus on the linear birth rate and rather treat it as a well-understood baseline case. Most of the analysis of this linear birth rate is in the Supplementary Information 2, and 3.

I find the formuation of (1-p) * nu * Is for dIw/dt and p * nu * Is for dIww/dt to be biologically hard to justify. It implies that there is some fixed rate of coinfection, when surely this should vary with the force of infection nu. The most rational way to define this would be either:
a) Changing the equations so that:
dI_w/dt = p1 *nu * I_s + ….
dI_ww / dt = p2 * nu * I_w + ….
This way first hosts must go through a single infection, and be exposed a second time to be doubly infected. This seems the most biologically defensible option. Although if the system entails immune memory formation, p2 < p1, these might just be set to some constant for simplicity. In this way, as the abundance of parasites in the environment gets low (nu ? 0), I_w becomes more common than I_ww, which is surely realistic.
b) Or, equivalently, the authors could allow simultaneous double infection as follows:
dI_w/dt = p *nu * I_s + ….

dI_ww / dt = p^2 * nu^2 * I_s + ….
This formulation also requires that two infectious particles reach a susceptible host, each having some probability p of establishing (the probability they both establish is then p^2)
c) Or, one could formally use a binomial probability, allowing 0, 1, or 2 infections to occur each with a binomial probability whose rate is dictated by the FOI

Actually, p is not the rate of coinfection but the probability of co-transmission from the parasite pool to the intermediate host, which varies from 0 to 1. We hope it is now clear via the updated flow figure and the associated description. The probability of co-transmission was used in a similar manner in Alizon et al 2012. When a susceptible intermediate host encounters the parasite pool, infection always happens. There is a probability p that two parasites get into the host together (double infection), and thus, there is a probability (1-p) that only one parasites get into the host (single infection). We mention that for simplification, we do not consider sequential infection in this stage, that is, the singly infected intermediate host will not be exposed a second time to be doubly infected, as suggested by the reviewer in scenario a).

The co-infection rate does depend on the force of infection because it would include the whole term p * eta (we would like to clarify here that the annotation in Greek is eta and not nu), where eta = gamma * W is the force of infection is the rate at which susceptible host got infected by the parasites. Here, gamma is the transmission rate of the free-living parasite, and W is the density of the free-living parasite.

A suggestion, keeping with two parameters but another way of framing it: Beta_w is the manipulation strategy when solo. This is modified by a multiplier when paired, for instance c*Beta_w where c represents the fold-change (reduction if c<1, increase if c>1) in Beta. Most of the important variation your paper investigates will probably be centered on the role of c, whereas if you focused on Beta_w and Beta_ww that isn't as clear

While it is appealing to introduce the parameter beta_ww = c * beta_w as suggested to simplify the narration it would come with additional assumptions and compromise the generality of our approach especially about the relationship between beta_w and beta_ww. Note that, we did this simplification for f_ww and f_w where f_ww = epsilon * f_w, as parasite reproduction is not our focal.

Introducing beta_ww = c * beta_w would mean an assumption of a linear relationship, whereas the relationship could very well be beta_ww = beta_w^c, or any other complicated function.

While the model is general indeed, we assume a linear relationship between beta_ww and beta_w in Figure 6, for the analysis of multiple parameters. However, if we initially state this as an assumption of the model then we lose generality. Taking into account the reviewer's suggestion we do mention this explicitly when we discuss figure 6 in line 261-264.

Reading the model description was difficult because there are many terms that are not defined (except in the table, that isn't even mentioned until the end of the Methods; examples include gamma, alpha), or defined late. At a minimum, refer to the table (and the diagram Figure 2) right at the start of the model description. The authors could also slim down the equations by replacing Is,Iw,Iww with I_total, replacing D_s D_w D_ww with D_total, and so on).

We realise that it is quite a challenge to read the model description. To ease the reader, we have now added explanations in the main text for clarification in line

117-121, 126-128, 134-136, and 144. In addition, following the reviewer's suggestion, we replace I_s, I_w, and I_ww with I_total and referring to the Table earlier in the model description.

Figure 2, if I might venture a comparison, is a bit of a bowl of spaghetti, with 9 different lines pointing in various directions. It looks messy and does not help reader comprehension. It also is missing missing Dw --> Dww arrow, and missing I_s and D_s. There's no indication of beta effects, or where various parameter symbols come into play. I think a cleaner visual layout could be achieved with a cycle (intermediate hosts top left, definitive hosts top right, parasite propagules bottom middle). That way the light blue arrows you have now go from 6-o'clock to 10 o'clock, the green infection arrows go from 10 o'clock to 2 o'clock, and the red arrows go from 2 o'clock to 6 o'clock.

We agree that the schematic for this model is rather tricky as it involves both predator-prey and parasitic relationships. In addition, the two relationships are entangled as predation means transmission. To make the schematic less messy, we needed to reduce some arrows, such as Dw —> Dww, as Dw needs to eat either Iw or Iww to become Dww. However now we have added this step with the joined arrows.

We also reorganised the symbols following trophic relationships with a free-living parasite pool at the bottom, intermediate hosts in the middle and definitive hosts at the top. In addition, we would like the audience to focus more on the transmission aspect, hence the omission of the susceptible symbols for intermediate and definitive hosts.

Contrary to reviewer 1 last time, I find the Methods / Results separation to be awkward and artificial in theory papers. For instance I think the equations on page 11, and the non-linear first host reproduction, are better defined in the Methods (or, as part of a streamlined narrative without artificial subdivision). I know the authors will feel caught between reviewers opposing views on this, and have already made a change in one direction. I suggest that the Editor provide their journal style policy as guidance here.

We agree with the reviewer. We also find it very artificial to separate the model from the results. We will wait for the comments from the editor since we first had the sections together, and then we changed it based on the previous referee's comments. According to what the journal recommends, we will then adhere to one style.

Line 187: unrealistic, destabilizing, and leads to oddly unstable outcomes, so why bother?

We discussed this issue in the previous comment. The unstable equilibrium is not odd and unrealistic but requires a different analysis technique.

Line 189: Jacobian should be capitalized I believe??

Done

Line 233: per my suggestion above, this could change to c > 1, allowing you to analyze the effects of one variable, rather than the effects of relative values of two variables, and line 234 c < 1

We have discussed this point in the previous comment

Line 259 (and the paragraph ending here). This is a very interesting set of combinatorial possibilities. Seems like selection should eliminate two of them from contention, if the parasites were to evolve. Just a thought. Evolutionary dynamics of beta_ww/beta_w and f_ww/f_w would be interesting to comment on in the discussion.

Again, we are fully sympathetic to the reviewer's concern about the evolutionary discussion. Previously, we had a larger section of the Discussion about the possible evolutionary dynamics of this system as a natural extension. It is very intuitive to think that if evolution is taken into account, selection would eliminate the scenario where parasites suppress reproduction and sabotage manipulation, as it is shown that this leads to the extinction of the parasite population. Note that the extinction of the parasite could also be an outcome, a phenomenon well-known as evolutionary suicide. However, it is quite a challenge to speculate different evolutionary outcomes as ecological feedback from intermediate and definitive hosts should also have an important influence.

The evolutionary dynamics also depend heavily on the relationship between manipulation and reproduction. For instance, parasites may produce fewer offspring if they invest in manipulation. That is why incorporating multiple infections in this model is important, as cooperation in the manipulation of multiple infections could reduce individual effort in manipulation.

For these reasons, we limit our discussion on evolution in this manuscript. It definitely deserves a careful analysis with specific assumptions for trade-offs.