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PROCEEDINGS B

Infectious disease and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils

David G. Hamilton, Menna E. Jones, Elissa Z. Cameron, Douglas H. Kerlin, Hamish McCallum, Andrew Storfer, Paul A. Hohenlohe and Rodrigo K. Hamede

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Review timeline
Original submission: 26 March 2020
1st revised submission: 2 October 2020
2nd revised submission: 10 November 2020
Final acceptance: 10 November 2020

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Review History

RSPB-2020-0676.R0 (Original submission)

Review form: Reviewer 1

Recommendation
Major revision is needed (please make suggestions in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Good

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
Yes

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
No

Is it clear?
No

Is it adequate?
No

Do you have any ethical concerns with this paper?
No

Comments to the Author
Review of RSPB-2020-0676: Cancer and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils
In this manuscript, Hamilton et al. investigate the question of whether and how sickness behavior affects an individual's contact behavior and whether the position of susceptible individuals within their social network affects disease risk. To address these questions, they use the fairly well-characterized system of devil facial tumour disease (DFTD) in Tasmanian devils.
Major comments:
This is an exciting study because it tackles an outstanding question in disease ecology of how sickness-induced behavioral changes can affect disease transmission. This has only been tackled in a few prior empirical systems, and the authors bring some new tools to bear on the question, particularly temporal exponential random graph models (tERGMs). Overall, I found this to be a timely study with novel application of ERGM approaches to a wildlife system.
My first major concern, which the authors allude to in their discussion, is the relative paucity of transmission events captured where a susceptible individual progresses to being infected during the duration of the study. This limits the ability of the authors to look at the effect of sex on the DFTD-infected individuals (per p. 24), but I also wonder if this is limiting the ability to parse out the effects of network position on transmission events (~85,000 interactions vs. a handful of infection events from ~20 individuals). This is a hugely informative data set, and I do not wish to imply that more data collection needs to occur, but I am wondering if this limitation can be discussed a little more clearly in the discussion where the authors conclude that a susceptible individual's position in the network has no bearing on subsequent infection risk. There exists a fair amount of literature about the causal relationship between infection status and network position in wildlife, and I make a few suggestions about that below.
My other major concern is the generalizability of DFTD as a model of cancer-induced behavior change, as the authors suggest throughout the introduction and discussion. The authors posit that DFTD is representative of "cancer" very broadly, but the unique nature of DFTD symptoms/presentation and etiology among cancers makes this rather a stretch, in my view. DFTD would seem to be a better model for behavioral responses to highly virulent diseases or diseases which severely affect the same body systems as DFTD. I find it difficult to believe that DFTD-induced behavioral change would be generalizable to, say, canine hemangiosarcoma. I think the authors—and the research—would be better served by presenting the research in the context of disease-induced behavioral change associated with "infectious disease" more

generally, rather than focusing on cancers.
Associated with the previous concern, I feel the authors need to better support their assertion of the high prevalence of cancers in wildlife. This is, of course, an understudied area of wildlife health, but even within zoological medicine, cancers are often not cited as a major/highly prevalent concern for many species. For example, Fowler's Zoo and Wildlife Medicine, a key text in zoological medicine, cites only DFTD among key noninfectious diseases of marsupials, with no other neoplastic disorders mentioned. Further, Vittecoq et al 2013 TREE point out that "the incidence of cancers in wildlife is poorly understood." Again, I feel that DFTD is a better model for infectious disease-induced behavioral change, especially given the uncertainty of the actual prevalence of neoplasias in wildlife. The current strong emphasis on the importance of cancers in wildlife requires much more discussion/support in the introduction, in particular.
-p. 8- Could you talk a little bit more about how and why you settled on a 14-day period for the analysis of network metrics? Is there a biological motivation for this period? How sensitive are these node-level metrics to different periods of aggregation?
Lastly, per the journal guidelines "It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository." The authors have stated that they will upload data to a Dryad repository, but right now it is not possible to verify the analyses or results for this manuscript. I would encourage the authors to make sure that code is reproducible and publically available to support this manuscript.
Minor comments:
- p. 2 (abstract)- what is meant by "knock-on effects"?
- p. 3 - The first sentence "Behavioral interactions are influenced…" sets up the reader to expect the paper to focus on the role of proximate and ultimate factors which is not the case. It may be better to clearly introduce examples of proximate and ultimate causes as they relate to this system or delete this sentence altogether as it does not relate well to the overall objective of the manuscript.
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the following sentence: "The disease severely impacts the health of infected individuals, particularly as tumour volume increases, resulting in immunocompromise, poor body condition and lack of competitiveness in resource acquisition [33]."

- p. 6, first paragraph - The use of 'switching' as the verb in the sentence "We used a series of network autocorrelation models…" is a strange choice. Perhaps something with more biological relevance such as 'converting' or even 'becoming infected' ?
- p. 7 last sentence- I would use colon rather than a hyphen to introduce the equation for tumor volume.
- p. 8, 2nd paragraph- why the choice to weight edges by frequency of contacts versus the duration of contacts? Is there a biologically/transmission relevant justification for this choice?.
- p. 8 last paragraph- for clarity, it would be best to specify that weighted degree is not just the number of individuals associated with a particular node, but that it is modulated by the relative strength of those interactions.
- p. 8 last paragraph - In addition, it would be more clear to refer to the metrics mentioned here (namely "total of number of interactions" and "weighted degree") using the same words later in the text (i.e. chose and be consistent with either "total number of interactions" or "interaction frequency" and either "weighted degree" or "degree"). These are mentioned later in the text using different wording: on p.11 second paragraph ("Interaction frequency differed significantly…" and "Degree was significantly lower in DFTD…" and p.14 Fig 2 legend ("a) interaction frequency b) degree…").
- p. 8 last paragraph-- I wonder are the definitions for betweenness and closeness clear enough for an audience not so savvy with contact networks. Adding the biological relevance of these network metrics could also be useful to clarify what makes betweenness and closeness centrality different in the context of devil social networks and why these could be important in DFTD transmission.
-p. 9 first paragraph- What do you mean by "nodes shuffled by disease status"? It's a little unclear whether it's the status of the nodes or the edges between nodes that are being randomized.
- p. 10- unlike the other network terms, clustering coefficient has not yet been defined.
- p. 10- could you please clarify what you mean by "all network terms were centred"- do you mean that all the values were normalized?
- p. 10- consider adding an additional sentence about what the weightlag() term is and how it accounts for network non-independence.The interpretation of the weightlag() term in the results section (p.18, first paragraph) suggests this term indicates the likelihood of individuals to interact with other individuals of the same disease status, but the initial explanation given on p.10 only mentions "the non-independence of connected individuals" and doesn't clarify the nature of this non-independence.
- p. 11, 2nd paragraph- what are the "f"s in the parenthetical model results? Are these the same as "F"s in Figure 1. Assumed that "f" corresponds to "Fortnight" but this was ever explicitly stated.
- Figure 1 legend:
  - this is nitpicking, but do you want to say that node size is "scaled" by category of tumor load?
  - Also unclear what the numbers in parentheses correspond to (e.g. 1= 0.0001-50 cm3). Does "1" mean 100% bigger?
  - It would also make sense to share any scaling that has been done to depict edge weight or explicitly state if no scaling has been performed.
  - Could you go ahead and remind the reader which fortnightly contact networks (F1-F12) correspond to mating vs. non-mating season?
- Figure 2: please add asterisks above significant differences. It is often difficult to see if CI bars are overlapping.
- p.16 The way the TERGMs were introduced on p.9 ("...used to investigate whether individual interaction patterns within a contact network differ as a result of infection status, tumor load, or number of bite wounds accrued…") implies that parallel analyses would be run for each of three factors (DFTD status, tumor load, and number of wounds). However, when the results are presented on p.16, the probability of edge formation with respect to DFTD infection and tumor load are discussed, but not with respect to bite wounds. Bite wounds is instead included as a

model term in both the models of DFTD status and tumor load (p.17 Table 1). There is a disconnect in how bite wounds are modeled between the methods presented on p.9 (bite wounds are presented as a factor on the same level as DFTD status and tumor load, influential in predicting edge formation) and the results presented on p.16 (bite wounds as a factor in the model (like 'sex' or 'memory') of the influence of DFTD status and tumor load in predicting edge formation). Clearer language about inputs and outputs would be helpful.

- p. 17 1st paragraph- just to clarify, by "sex-mixing" you are referring to propensity to mix with same or different sex (i.e. homophily) in Table 1?
- p. 18, 1st sentence - For clarity, I would suggest "network metrics examined by season" as opposed to "seasonal network metrics"
- p. 18, 1st sentence- I think "devil's" should be " devils' " as you are referring to predictors for all devils.
- p. 19- I think the conclusion that "the network position of healthy animals had no clear influence on their likelihood of developing clinical signs of DFTD in the short-term." could use some additional context with existing literature. This is a question that has been investigated fairly extensively in wildlife to date. For example:
  - o (Corner et al., 2003): for brushtail possums experimentally infected with bTB, animals that naturally contracted bTB from experimentally infected individuals were more likely to be central to the network. Specifically, they had higher closeness and flow-betweenness scores relative to individuals that did not become infected naturally.
  - o (Drewe, 2010): meerkats more central to the network were not de facto more likely to be infected with bTB
- p. 20- in the sentence, "[...] particularly at high tumour volumes, indicates a threshold beyond which the effect of cancer on behaviour becomes pronounced." This is an example where the authors have overgeneralized "cancer," as not all cancers are associated with tumor volume, per se (e.g. blood cancers).
- p 20 2nd paragraph: Is body condition being used as evidence of decreased competitive ability/is body condition linked to behavior in this comparison? That would be a hard factor to isolate from cancer cachexia.
- p 20 end of 2nd paragraph-- Are DFTD (+) individuals infrequently interacting or just less frequently than others? This has an impact on your assertion in the next paragraph
- p. 20- why are individuals expected to be most likely to transmit DFTD when tumours are at their largest? Can you cite or explain this reasoning more?
- p 21 in sentence "Secondly, if any avoidance behaviour occurs in healthy animals, their poor condition and requirement for sustenance may now outweigh the potential costs of interacting with an infected individual"-- Why would an individuals poor condition and hunger make it more likely to interact/stop avoiding sick individuals? Less energy to fend them off or be choosy with a mate? Would they not be just searching for food solitarily? I may not know enough about devils. Also wondering how this leads into the next sentence "Thus there is….". I would like to see references to your data supporting this. Overall, while the analysis on p.21 presents an interesting and potentially important implication of DFTD transmission revealed by this study, the arguments presented lack clarity. More clear wording should be used to identify if the authors are referring to interactions between infected and healthy individuals via competition for mates or food resources (or both). While both of these may occur and be important for transmission, the argument as written blends these two drivers of interactions in a way that confuses and weakens the argument.
- p. 21- I'm not sure the results shown in figure 2 really support the conclusion that late-season interactions would be "critical." The differences shown in figure 2 don't exhibit a particularly strong/consistent pattern, especially for calling the effect "critical" (depending on the network metric considered, DFTD and healthy individuals overlap for 1 or 2/5 to 5/5 fortnightly timesteps during the mating season).
- p. 22- capitalize "dasyurids" if referring to taxonomic family?
- p. 22- it seems that GPS and/or accelerometer data would have been helpful to try to detect evidence of avoidance behavior or changes in activity levels. I'm not proposing that more data need be collected for this study, but this could be a useful future direction to mention/limitation of the current study.

- p. 22, 2nd paragraph- the references supporting sex-sppecific differences in infection and cancer costs/survival seem to be quite limited, especially given the extremely broad scope of this statement. .
- p22- Was it only one F-F pair that remained together after one became infected?
- p. 23- another interesting study to discuss in the context of behavioral avoidance might be: (Croft et al., 2011): explored how groups of fish reacted to the introduction of either an infected or uninfected individual. They found that infected guppies associated less with the group than their uninfected counterparts.
- p. 23, concluding paragraph- "It is considered [...]" consider rewording for more strong/active phrasing. Additionally, this sentence should go in the introduction, rather than the final paragraph, to support the highly unusual case of DFTD as a model of cancers in other species. Even with moving this sentence, however, I still feel that DFTD is a poor model of cancer-induced behavioral change in the extremely broad context the authors have used throughout.

Works cited in review:

Corner, L. A. L., Pfeiffer, D. U., & Morris, R. S. (2003). Social-network analysis of Mycobacterium bovis transmission among captive brushtail possums (Trichosurus vulpecula). Preventive Veterinary Medicine, 59(3), 147–167. https://doi.org/10.1016/S0167-5877(03)00075-8
Croft, D. P., Edenbrow, M., Darden, S. K., Ramnarine, I. W., van Oosterhout, C., & Cable, J. (2011). Effect of gyrodactylid ectoparasites on host behaviour and social network structure in guppies Poecilia reticulata. Behavioral Ecology and Sociobiology, 65(12), 2219–2227. https://doi.org/10.1007/s00265-011-1230-2
Drewe, J. A. (2010). Who infects whom? Social networks and tuberculosis transmission in wild meerkats. Proceedings of the Royal Society B, 277(1681), 633–642. https://doi.org/10.1098/rspb.2009.1775
Vittecoq, M., Roche, B., Daoust, S. P., Ducasse, H., Missé, D., Abadie, J., ... & Thomas, F. (2013). Cancer: a missing link in ecosystem functioning?. Trends in ecology & evolution, 28(11), 628-635. https://doi.org/10.1016/j.tree.2013.07.005
White, L. A. L. A., Forester, J. D. J. D., & Craft, M. E. M. E. (2018). Covariation between the physiological and behavioral components of pathogen transmission: host heterogeneity determines epidemic outcomes. Oikos, 127(4), 538–552. https://doi.org/10.1111/oik.04527

Review form: Reviewer 2 (Frederic Thomas)

Recommendation
Accept with minor revision (please list in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Excellent

General interest: Is the paper of sufficient general interest?
Good

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
Yes

Is it clear?
Yes

Is it adequate?
Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
Comments on the paper entitled: Cancer and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils. By David G. Hamilton a, Menna E. Jones a, Elissa Z. Cameron a,b, Douglas H. Kerlin c, Hamish McCallum c, Andrew Storfer d, Paul A. Hohenlohe e, and Rodrigo K. Hamede

In this study, Hamilton et al. explored the links between a transmissible cancer (DFTD) and the behaviour of its host, the Tasmanian devil. First, they assess how interaction patterns within the host social network is altered with the growth of tumors. They then explored whether devil interaction patterns influence the probability of susceptible individuals to present clinical signs of DFTD in the short-term. Their results show that the presence of malignancies negatively influences devils' likelihood of interaction, and this is amplified with tumour growth. There was no effect of the individual's position within their social network and likelihood that individuals present clinical signs of the cancer within six months.

This is a fascinating and very original study, that obviously necessitated a hard field work. Methods are elegant and well explained.

I only have minor comments on this beautiful work
1) Introduction, first sentence: "Behavioural interactions are influenced…" you mean Behavioural interactions between individuals ? species ? please precise.
2) Introduction, at the end of the first paragraph, maybe authors could also cite this reference:
Ezenwa VO, Archie EA, Craft ME, Hawley DM, Martin LB, Moore J, White L. 2016 Host behaviour-parasite feedback: An essential link between animal behaviour and disease ecology. Proc. R. Soc. B Biol. Sci. (doi:10.1098/rspb.2015.3078)
3) Introduction, the first sentence of the second paragraph.
The sentence "Behavioural responses to infection are the result of two interacting factors – avoidance of disease carriers by healthy individuals and disease-induced changes in behaviour of infected individuals." Should be:

The sentence "Behavioural responses to infection are the result of AT LEAST two interacting factors – avoidance of disease carriers by healthy individuals and disease-induced changes in behaviour of infected individuals (Moore 2002)."

Indeed, there is a HUGE literature on host-manipulation by parasites. There is also self medication phenomena, sometimes self sacrifice, see (4). I understand that this is not the direct topic of your study, but you cannot in opinion reduce your statement like that, as it is a bit naïve and/or it suggests that you are voluntarily ignoring these important phenomena.

You could also cite the book by Janice Moore (Parasites and the Behaviour of animals, Oxford university press 2002).

Also, sometimes a given behavior is both the cause and the consequence of the infection, see for instance the two references below. You should also mention these situations in your introduction and/or your discussion.
Blanchet S, Méjean L, Bourque JF, Lek S, Thomas F, Marcogliese DJ, Dodson JJ, Loot G. 2009 Why do parasitized hosts look different? Resolving the 'chicken- egg' dilemma. Oecologia (doi:10.1007/s00442-008-1272-y)

Blanchet S, Thomas F, Loot G. 2009 Reciprocal effects between host phenotype and pathogens: new insights from an old problem. Trends Parasitol. (doi:10.1016/j.pt.2009.05.005)

4) Sentence between page 3-4; Sometimes social isolation also permits to prevent the infection of kin related individuals (e.g. self sacrifice, e.g. Shorter JR, Rueppell O. 2012 A review on self-destructive defense behaviors in social insects. Insectes Soc. (doi:10.1007/s00040-011-0210-x)
5) End of page 4, I am not sure that cancer is always "highly virulent" among animals (even in humans, the more we get old the more we have for instance in situ carcinoma without significant health effect). I would thus change the sentence: "Studying the behavioural effects of oncogenic processes in wild populations is both ecologically and epidemiologically relevant across a broad range of taxa, as cancer is a highly virulent and ubiquitous disease present in most multicellular organisms [25]. By "Given the ubiquity of oncogenic processes in most multicellular organisms [25], studying their behavioural effects in wild populations is both ecologically and epidemiologically relevant across a broad range of taxa."
6) Page 21, given that the behavioural changes you observe are apparently 'good' for the cancer transmission, is it possible that the patterns you observe results from a host manipulation by DFTD to favour its transmission ? After all, many parasites develop strategies for their transmission, including the way they induce pathological consequences on the host, if this is good for the transmission...

As you understood, I I would suggest that in your introduction you give a more complete panorama of the complexity of the relationships between host behavior and parasites (see my previous comments), and then that you could better discuss your results in this perspective, mentioning for instance the manipulation hypothesis (if relevant for you of course)…

Else, congratulations for this beautiful work !
F. Thomas

Decision letter (RSPB-2020-0676.R0)

10-May-2020

Dear Mr Hamilton:

I am writing to inform you that your manuscript RSPB-2020-0676 entitled "Cancer and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils" has, in its current form, been rejected for publication in Proceedings B.

This action has been taken on the advice of referees, who have recommended that substantial revisions are necessary. With this in mind we would be happy to consider a resubmission, provided the comments of the referees are fully addressed. However please note that this is not a provisional acceptance.

The resubmission will be treated as a new manuscript. However, we will approach the same reviewers if they are available and it is deemed appropriate to do so by the Editor. Please note that resubmissions must be submitted within six months of the date of this email. In exceptional circumstances, extensions may be possible if agreed with the Editorial Office. Manuscripts submitted after this date will be automatically rejected.

Please find below the comments made by the referees, not including confidential reports to the Editor, which I hope you will find useful. If you do choose to resubmit your manuscript, please upload the following:

1) A 'response to referees' document including details of how you have responded to the comments, and the adjustments you have made.
2) A clean copy of the manuscript and one with 'tracked changes' indicating your 'response to referees' comments document.
3) Line numbers in your main document.

To upload a resubmitted manuscript, log into http://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Resubmission." Please be sure to indicate in your cover letter that it is a resubmission, and supply the previous reference number.

Sincerely,
Professor Hans Heesterbeek
mailto: proceedingsb@royalsociety.org

Associate Editor
Board Member: 1
Comments to Author:
Please carefully consider the suggestions made in the two detailed reviews received on this manuscript, paying particular attention to issues raised concerning the number of observations of contacts that could lead to transmission events and whether to consider DFTD as a representative model for transmissible cancers vs other infectious processes in wildlife.

Reviewer(s)' Comments to Author:
Referee: 1
Comments to the Author(s)
Review of RSPB-2020-0676: Cancer and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils
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Minor comments:

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- p. 5, 2nd paragraph - "Transmission is driven by the social and aggressive behavior of the species…" It may be useful to link this statement more directly to the occurrence of biting/fighting behavior relevant to transmission and when/how this occurs in devils (and if it is expected to vary seasonally). For example: is there more intra-sex over mates or is biting a part of mating behavior (inter-sex transmission) making transmission more likely during the breeding season? Or is competition over food a common source of bite interactions and therefore transmission probability is high year-round?
- p. 5, 2nd paragraph- I think "immunocomprise" needs to be "immunocompromisation" in the following sentence: "The disease severely impacts the health of infected individuals, particularly as tumour volume increases, resulting in immunocompromise, poor body condition and lack of competitiveness in resource acquisition [33]."
- p. 6, first paragraph - The use of 'switching' as the verb in the sentence "We used a series of network autocorrelation models…" is a strange choice. Perhaps something with more biological relevance such as 'converting' or even 'becoming infected' ?
- p. 7 last sentence- I would use colon rather than a hyphen to introduce the equation for tumor volume.
- p. 8, 2nd paragraph- why the choice to weight edges by frequency of contacts versus the duration of contacts? Is there a biologically/transmission relevant justification for this choice?.
- p. 8 last paragraph- for clarity, it would be best to specify that weighted degree is not just the number of individuals associated with a particular node, but that it is modulated by the relative strength of those interactions.
- p. 8 last paragraph - In addition, it would be more clear to refer to the metrics mentioned here (namely "total of number of interactions" and "weighted degree") using the same words later in the text (i.e. chose and be consistent with either "total number of interactions" or "interaction frequency" and either "weighted degree" or "degree"). These are mentioned later in the text using different wording: on p.11 second paragraph ("Interaction frequency differed significantly…" and "Degree was significantly lower in DFTD…" and p.14 Fig 2 legend ("a) interaction frequency b) degree…").
- p. 8 last paragraph-- I wonder are the definitions for betweenness and closeness clear enough for an audience not so savvy with contact networks. Adding the biological relevance of these network metrics could also be useful to clarify what makes betweenness and closeness centrality different in the context of devil social networks and why these could be important in DFTD transmission.
-p. 9 first paragraph- What do you mean by "nodes shuffled by disease status"? It's a little unclear whether it's the status of the nodes or the edges between nodes that are being randomized.
- p. 10- unlike the other network terms, clustering coefficient has not yet been defined.
- p. 10- could you please clarify what you mean by "all network terms were centred"- do you mean that all the values were normalized?
- p. 10- consider adding an additional sentence about what the weightlag() term is and how it accounts for network non-independence.The interpretation of the weightlag() term in the results section (p.18, first paragraph) suggests this term indicates the likelihood of individuals to interact with other individuals of the same disease status, but the initial explanation given on p.10 only

mentions "the non-independence of connected individuals" and doesn't clarify the nature of this non-independence.

- p. 11, 2nd paragraph- what are the "f"s in the parenthetical model results? Are these the same as "F"s in Figure 1. Assumed that "f" corresponds to "Fortnight" but this was ever explicitly stated.
- Figure 1 legend:
  - this is nitpicking, but do you want to say that node size is "scaled" by category of tumor load?
  - Also unclear what the numbers in parentheses correspond to (e.g. 1= 0.0001-50 cm3). Does "1" mean 100% bigger?
  - It would also make sense to share any scaling that has been done to depict edge weight or explicitly state if no scaling has been performed.
  - Could you go ahead and remind the reader which fortnightly contact networks (F1-F12) correspond to mating vs. non-mating season?
- Figure 2: please add asterisks above significant differences. It is often difficult to see if CI bars are overlapping.
- p.16 The way the TERGMs were introduced on p.9 ("...used to investigate whether individual interaction patterns within a contact network differ as a result of infection status, tumor load, or number of bite wounds accrued…") implies that parallel analyses would be run for each of three factors (DFTD status, tumor load, and number of wounds). However, when the results are presented on p.16, the probability of edge formation with respect to DFTD infection and tumor load are discussed, but not with respect to bite wounds. Bite wounds is instead included as a model term in both the models of DFTD status and tumor load (p.17 Table 1). There is a disconnect in how bite wounds are modeled between the methods presented on p.9 (bite wounds are presented as a factor on the same level as DFTD status and tumor load, influential in predicting edge formation) and the results presented on p.16 (bite wounds as a factor in the model (like 'sex' or 'memory') of the influence of DFTD status and tumor load in predicting edge formation). Clearer language about inputs and outputs would be helpful.
- p. 17 1st paragraph- just to clarify, by "sex-mixing" you are referring to propensity to mix with same or different sex (i.e. homophily) in Table 1?
- p. 18, 1st sentence - For clarity, I would suggest "network metrics examined by season" as opposed to "seasonal network metrics"
- p. 18, 1st sentence- I think "devil's" should be " devils' " as you are referring to predictors for all devils.
- p. 19- I think the conclusion that "the network position of healthy animals had no clear influence on their likelihood of developing clinical signs of DFTD in the short-term." could use some additional context with existing literature. This is a question that has been investigated fairly extensively in wildlife to date. For example:
  - (Corner et al., 2003): for brushtail possums experimentally infected with bTB, animals that naturally contracted bTB from experimentally infected individuals were more likely to be central to the network. Specifically, they had higher closeness and flow-betweenness scores relative to individuals that did not become infected naturally.
  - (Drewe, 2010): meerkats more central to the network were not de facto more likely to be infected with bTB
- p. 20- in the sentence, "[...] particularly at high tumour volumes, indicates a threshold beyond which the effect of cancer on behaviour becomes pronounced." This is an example where the authors have overgeneralized "cancer," as not all cancers are associated with tumor volume, per se (e.g. blood cancers).
- p 20 2nd paragraph: Is body condition being used as evidence of decreased competitive ability/is body condition linked to behavior in this comparison? That would be a hard factor to isolate from cancer cachexia.
- p 20 end of 2nd paragraph-- Are DFTD (+) individuals infrequently interacting or just less frequently than others? This has an impact on your assertion in the next paragraph
- p. 20- why are individuals expected to be most likely to transmit DFTD when tumours are at their largest? Can you cite or explain this reasoning more?
- p 21 in sentence "Secondly, if any avoidance behaviour occurs in healthy animals, their poor condition and requirement for sustenance may now outweigh the potential costs of interacting

with an infected individual"-- Why would an individuals poor condition and hunger make it more likely to interact/stop avoiding sick individuals? Less energy to fend them off or be choosy with a mate? Would they not be just searching for food solitarily? I may not know enough about devils. Also wondering how this leads into the next sentence "Thus there is….". I would like to see references to your data supporting this. Overall, while the analysis on p.21 presents an interesting and potentially important implication of DFTD transmission revealed by this study, the arguments presented lack clarity. More clear wording should be used to identify if the authors are referring to interactions between infected and healthy individuals via competition for mates or food resources (or both). While both of these may occur and be important for transmission, the argument as written blends these two drivers of interactions in a way that confuses and weakens the argument.

- p. 21- I'm not sure the results shown in figure 2 really support the conclusion that late-season interactions would be "critical." The differences shown in figure 2 don't exhibit a particularly strong/consistent pattern, especially for calling the effect "critical" (depending on the network metric considered, DFTD and healthy individuals overlap for 1 or 2/5 to 5/5 fortnightly timesteps during the mating season).
- p. 22- capitalize "dasyurids" if referring to taxonomic family?
- p. 22- it seems that GPS and/or accelerometer data would have been helpful to try to detect evidence of avoidance behavior or changes in activity levels. I'm not proposing that more data need be collected for this study, but this could be a useful future direction to mention/limitation of the current study.
- p. 22, 2nd paragraph- the references supporting sex-sppecific differences in infection and cancer costs/survival seem to be quite limited, especially given the extremely broad scope of this statement. .
- p22- Was it only one F-F pair that remained together after one became infected?
- p. 23- another interesting study to discuss in the context of behavioral avoidance might be: (Croft et al., 2011): explored how groups of fish reacted to the introduction of either an infected or uninfected individual. They found that infected guppies associated less with the group than their uninfected counterparts.
- p. 23, concluding paragraph- "It is considered [...]" consider rewording for more strong/active phrasing. Additionally, this sentence should go in the introduction, rather than the final paragraph, to support the highly unusual case of DFTD as a model of cancers in other species. Even with moving this sentence, however, I still feel that DFTD is a poor model of cancer-induced behavioral change in the extremely broad context the authors have used throughout.

Works cited in review:

Corner, L. A. L., Pfeiffer, D. U., & Morris, R. S. (2003). Social-network analysis of Mycobacterium bovis transmission among captive brushtail possums (Trichosurus vulpecula). Preventive Veterinary Medicine, 59(3), 147–167. https://doi.org/10.1016/S0167-5877(03)00075-8

Croft, D. P., Edenbrow, M., Darden, S. K., Ramnarine, I. W., van Oosterhout, C., & Cable, J. (2011). Effect of gyrodactylid ectoparasites on host behaviour and social network structure in guppies Poecilia reticulata. Behavioral Ecology and Sociobiology, 65(12), 2219–2227. https://doi.org/10.1007/s00265-011-1230-2

Drewe, J. A. (2010). Who infects whom? Social networks and tuberculosis transmission in wild meerkats. Proceedings of the Royal Society B, 277(1681), 633–642. https://doi.org/10.1098/rspb.2009.1775

Vittecoq, M., Roche, B., Daoust, S. P., Ducasse, H., Missé, D., Abadie, J., ... & Thomas, F. (2013). Cancer: a missing link in ecosystem functioning?. Trends in ecology & evolution, 28(11), 628-635. https://doi.org/10.1016/j.tree.2013.07.005

White, L. A. L. A., Forester, J. D. J. D., & Craft, M. E. M. E. (2018). Covariation between the physiological and behavioral components of pathogen transmission: host heterogeneity determines epidemic outcomes. Oikos, 127(4), 538–552. https://doi.org/10.1111/oik.04527

Referee: 2

Comments to the Author(s)
Comments on the paper entitled: Cancer and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils. By David G. Hamilton a, Menna E. Jones a, Elissa Z. Cameron a,b, Douglas H. Kerlin c, Hamish McCallum c, Andrew Storfer d, Paul A. Hohenlohe e, and Rodrigo K. Hamede

In this study, Hamilton et al. explored the links between a transmissible cancer (DFTD) and the behaviour of its host, the Tasmanian devil. First, they assess how interaction patterns within the host social network is altered with the growth of tumors. They then explored whether devil interaction patterns influence the probability of susceptible individuals to present clinical signs of DFTD in the short-term. Their results show that the presence of malignancies negatively influences devils' likelihood of interaction, and this is amplified with tumour growth. There was no effect of the individual's position within their social network and likelihood that individuals present clinical signs of the cancer within six months.

This is a fascinating and very original study, that obviously necessitated a hard field work. Methods are elegant and well explained.

I only have minor comments on this beautiful work

1) Introduction, first sentence: "Behavioural interactions are influenced…" you mean Behavioural interactions between individuals ? species ? please precise.
2) Introduction, at the end of the first paragraph, maybe authors could also cite this reference: Ezenwa VO, Archie EA, Craft ME, Hawley DM, Martin LB, Moore J, White L. 2016 Host behaviour-parasite feedback: An essential link between animal behaviour and disease ecology. Proc. R. Soc. B Biol. Sci. (doi:10.1098/rspb.2015.3078)
3) Introduction, the first sentence of the second paragraph.
The sentence "Behavioural responses to infection are the result of two interacting factors – avoidance of disease carriers by healthy individuals and disease-induced changes in behaviour of infected individuals." Should be:

The sentence "Behavioural responses to infection are the result of AT LEAST two interacting factors – avoidance of disease carriers by healthy individuals and disease-induced changes in behaviour of infected individuals (Moore 2002)."

Indeed, there is a HUGE literature on host-manipulation by parasites. There is also self medication phenomena, sometimes self sacrifice, see (4). I understand that this is not the direct topic of your study, but you cannot in opinion reduce your statement like that, as it is a bit naïve and/or it suggests that you are voluntarily ignoring these important phenomena.

You could also cite the book by Janice Moore (Parasites and the Behaviour of animals, Oxford university press 2002).

Also, sometimes a given behavior is both the cause and the consequence of the infection, see for instance the two references below. You should also mention these situations in your introduction and/or your discussion.
Blanchet S, Méjean L, Bourque JF, Lek S, Thomas F, Marcogliese DJ, Dodson JJ, Loot G. 2009 Why do parasitized hosts look different? Resolving the 'chicken- egg' dilemma. Oecologia (doi:10.1007/s00442-008-1272-y)

Blanchet S, Thomas F, Loot G. 2009 Reciprocal effects between host phenotype and pathogens: new insights from an old problem. Trends Parasitol. (doi:10.1016/j.pt.2009.05.005)

4) Sentence between page 3-4; Sometimes social isolation also permits to prevent the infection of kin related individuals (e.g. self sacrifice, e.g. Shorter JR, Rueppell O. 2012 A review on self-destructive defense behaviors in social insects. Insectes Soc. (doi:10.1007/s00040-011-0210-x)
5) End of page 4, I am not sure that cancer is always "highly virulent" among animals (even in humans, the more we get old the more we have for instance in situ carcinoma without significant health effect). I would thus change the sentence: "Studying the behavioural effects of oncogenic processes in wild populations is both ecologically and epidemiologically relevant across a broad range of taxa, as cancer is a highly virulent and ubiquitous disease present in most multicellular organisms [25]. By "Given the ubiquity of oncogenic processes in most multicellular organisms [25], studying their behavioural effects in wild populations is both ecologically and epidemiologically relevant across a broad range of taxa."
6) Page 21, given that the behavioural changes you observe are apparently 'good' for the cancer transmission, is it possible that the patterns you observe results from a host manipulation by DFTD to favour its transmission ? After all, many parasites develop strategies for their transmission, including the way they induce pathological consequences on the host, if this is good for the transmission...

As you understood, I I would suggest that in your introduction you give a more complete panorama of the complexity of the relationships between host behavior and parasites (see my previous comments), and then that you could better discuss your results in this perspective, mentioning for instance the manipulation hypothesis (if relevant for you of course)…

Else, congratulations for this beautiful work !
F. Thomas

Author's Response to Decision Letter for (RSPB-2020-0676.R0)

See Appendix A.

RSPB-2020-2454.R0

Review form: Reviewer 1

Recommendation
Accept with minor revision (please list in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Excellent

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Excellent

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
No

Is it clear?
No

Is it adequate?
No

Do you have any ethical concerns with this paper?
No

Comments to the Author
I appreciate the authors' thoughtful engagement with my original comments and their patience with my lack of specific familiarity with the DFTD/Tasmanian devil system. The authors have adequately addressed all my concerns, and upon a second reread, I believe that the broadening of the intro to focus on sickness behaviors and streamlining of the analysis makes the paper more broadly applicable to other systems and strengthens the storyline. Nice work!

My only final concern is that the doi link for the data/analysis materials is returning a "doi not found" error. Best to verify/confirm before proceeding (perhaps it's just me, or will be released upon acceptance).

Review form: Reviewer 2 (Frederic Thomas)

Recommendation
Accept as is

Scientific importance: Is the manuscript an original and important contribution to its field?
Excellent

General interest: Is the paper of sufficient general interest?
Good

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
Yes

Is it clear?
Yes

Is it adequate?
Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
The amended version has been considerably improved. Authors have adressed adequatly my comments

Decision letter (RSPB-2020-2454.R0)

06-Nov-2020

Dear Mr Hamilton

I am pleased to inform you that your nice manuscript RSPB-2020-2454 entitled "Infectious disease and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils" has been accepted for publication in Proceedings B.

The referees have recommended publication, but also suggest one important revision to your manuscript. Therefore, I invite you to respond to the comment and revise your manuscript accordingly. Because the schedule for publication is very tight, it is a condition of publication that you submit the revised version of your manuscript within 7 days. If you do not think you will be able to meet this date please let us know.

To revise your manuscript, log into https://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript and upload a new version through your Author Centre.

When submitting your revised manuscript, you will be able to respond to the comments made by the referee(s) and upload a file "Response to Referees". You can use this to document any changes you make to the original manuscript. We require a copy of the manuscript with revisions made since the previous version marked as ‘tracked changes’ to be included in the ‘response to referees’ document.

Before uploading your revised files please make sure that you have:

1) A text file of the manuscript (doc, txt, rtf or tex), including the references, tables (including captions) and figure captions. Please remove any tracked changes from the text before submission. PDF files are not an accepted format for the "Main Document".

2) A separate electronic file of each figure (tiff, EPS or print-quality PDF preferred). The format should be produced directly from original creation package, or original software format. PowerPoint files are not accepted.

3) Electronic supplementary material: this should be contained in a separate file and where possible, all ESM should be combined into a single file. All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI.

Online supplementary material will also carry the title and description provided during submission, so please ensure these are accurate and informative. Note that the Royal Society will not edit or typeset supplementary material and it will be hosted as provided. Please ensure that the supplementary material includes the paper details (authors, title, journal name, article DOI). Your article DOI will be 10.1098/rspb.[paper ID in form xxxx.xxxx e.g. 10.1098/rspb.2016.0049].

4) A media summary: a short non-technical summary (up to 100 words) of the key findings/importance of your manuscript.

5) Data accessibility section and data citation
It is a condition of publication that data supporting your paper are made available either in the electronic supplementary material or through an appropriate repository (https://royalsociety.org/journals/authors/author-guidelines/#data).

In order to ensure effective and robust dissemination and appropriate credit to authors the dataset(s) used should be fully cited. To ensure archived data are available to readers, authors should include a 'data accessibility' section immediately after the acknowledgements section. This should list the database and accession number for all data from the article that has been made publicly available, for instance:
• DNA sequences: Genbank accessions F234391-F234402
• Phylogenetic data: TreeBASE accession number S9123
• Final DNA sequence assembly uploaded as online supplemental material
• Climate data and MaxEnt input files: Dryad doi:10.5521/dryad.12311
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Once again, thank you for submitting your manuscript to Proceedings B and I look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Sincerely,
Professor Hans Heesterbeek
mailto: proceedingsb@royalsociety.org

Associate Editor
Board Member
Comments to Author:
I commend the authors for their very thorough revision of their manuscript in response to the highly detailed and expert reviews they received. I agree with the reviewers that the manuscript is greatly improved, pending a working link to the data repository (as indicated by a reviewer, the link provided returns an error message).

Reviewer(s)' Comments to Author:
Referee: 2
Comments to the Author(s).
The amended version has been considerably improved. Authors have addressed adequately my comments.

Referee: 1
Comments to the Author(s).
I appreciate the authors' thoughtful engagement with my original comments and their patience with my lack of specific familiarity with the DFTD/Tasmanian devil system. The authors have adequately addressed all my concerns, and upon a second reread, I believe that the broadening of the intro to focus on sickness behaviors and streamlining of the analysis makes the paper more broadly applicable to other systems and strengthens the storyline. Nice work!

My only final concern is that the doi link for the data/analysis materials is returning a "doi not found" error. Best to verify/confirm before proceeding (perhaps it's just me, or will be released upon acceptance).

Author's Response to Decision Letter for (RSPB-2020-2454.R0)

See Appendix B.

Decision letter (RSPB-2020-2454.R1)

10-Nov-2020

Dear Dr Hamilton

I am pleased to inform you that your manuscript entitled "Infectious disease and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils" has been accepted for publication in Proceedings B.

You can expect to receive a proof of your article from our Production office in due course, please check your spam filter if you do not receive it. PLEASE NOTE: you will be given the exact page

length of your paper which may be different from the estimation from Editorial and you may be asked to reduce your paper if it goes over the 10 page limit.

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Thank you for your fine contribution. On behalf of the Editors of the Proceedings B, we look forward to your continued contributions to the Journal.

Sincerely,
Editor, Proceedings B
mailto: proceedingsb@royalsociety.org

Appendix A

Response to Proc B reviewers – Infectious disease & sickness behaviour manuscript

Reviewer 1

Comment 1 - My first major concern, which the authors allude to in their discussion, is the relative paucity of transmission events captured where a susceptible individual progresses to being infected during the duration of the study. This limits the ability of the authors to look at the effect of sex on the DFTD-infected individuals (per p. 24), but I also wonder if this is limiting the ability to parse out the effects of network position on transmission events (~85,000 interactions vs. a handful of infection events from ~20 individuals). This is a hugely informative data set, and I do not wish to imply that more data collection needs to occur, but I am wondering if this limitation can be discussed a little more clearly in the discussion where the authors conclude that a susceptible individual's position in the network has no bearing on subsequent infection risk. There exists a fair amount of literature about the causal relationship between infection status and network position in wildlife, and I make a few suggestions about that below.

Response 1 - We appreciate the comment that "This is a hugely informative dataset…". As the reviewer mentions, despite the very large number (8,504) of interactions recorded, the sample size (in terms of individuals [22] and actual new infections [7]) is small. Given the low population density of Tasmanian devils once disease takes hold in a population, we think this data set represents as detailed a look as is feasible to get into Tasmanian devil social interactions. Most importantly, as we collared every adult individual in the population, the collars should have accurately recorded the number of interactions and potential transmission events in this population during the study period, and should also be representative of what would occur in other Tasmanian devil populations. To address this comment, we have tightened the scope of the paper so that its focus is on disease-mediated behavioural changes. This means we have removed the Network Autocorrelation Analysis (and all reference to it) that examined how network position related to infection risk. We may include it in a future manuscript which examines susceptibility and network position more closely, rather than including it here where it distracts from the main focus of the paper. We hope that the reviewers agree that this helps the focus and narrative flow of the manuscript.

Comment 2 - My other major concern is the generalizability of DFTD as a model of cancer-induced behavior change, as the authors suggest throughout the introduction and discussion. The authors posit that DFTD is representative of "cancer" very broadly, but the unique nature of DFTD symptoms/presentation and etiology among cancers makes this rather a stretch, in my view. DFTD would seem to be a better model for behavioral responses to highly virulent diseases or diseases which severely affect the same body systems as DFTD. I find it difficult to believe that DFTD-induced behavioral change would be generalizable to, say, canine hemangiosarcoma. I think the authors—and the research—would be better served by presenting the research in the context of disease-

induced behavioral change associated with “infectious disease” more generally, rather than focusing on cancers.

Response 2 - This is a very reasonable concern, which comes up quite a bit in framing of DFTD-focused studies. DFTD is in an interesting space, as an extremely lethal infectious disease which happens to be a cancer – this means it can be framed both as an infectious disease model, and as a model to study the effects of cancer in wildlife. DFTD progression follows the generalities of most cancers (including blood cancers etc.) with malignant cells proliferating uncontrollably, physiological costs increasing, leading to metabolic starvation and ultimately death – this makes it as good a model as any for the effects of cancer in general. The unusual aspect about this cancer is that transmission occurs via direct contact (biting) between infected and susceptible individuals, which is where the wider applicability to infectious diseases comes in. Thus, DFTD is a good model in both scenarios. We acknowledge that a strong emphasis was placed on the cancer aspect in the previous manuscript. We have now made several alterations (along with others, detailed later in the specific reviewer comments associated with them) to balance both aspects of the disease:

Line 22 – changed first sentence to “Infectious diseases, including transmissible cancers, can have a broad range of impacts on host behaviour”

Line 24 – changed “cancer” for “disease”

Line 33 – replaced “cancer” with “disease”

Line 92 – replaced “Studying behavioural changes as a result of cancer in wildlife…” with “Studying sickness behaviour in wildlife…”

Line 300 – Replaced “cancer-induced” with “disease-induced”

Line 381 – Final paragraph now reads: “Evaluating the effects of disease on behaviour is rare in wildlife studies, owing to the difficulty of diagnosis and following disease progression in a wild setting. Here we provide evidence that progression of a transmissible cancer alters interaction rates and position within a social network in Tasmanian devils. This has implications for our understanding of how infectious cancers may evolve and spread. 15 - 20% of cancers in humans [58], possibly even more in wildlife [59], have been associated with direct infectious origins. Improved knowledge of the behavioural side-effects of infectious diseases can help to further understand their overall ecological and evolutionary effects in wildlife across a broad range of taxa.”

Comment 3 - Associated with the previous concern, I feel the authors need to better support their assertion of the high prevalence of cancers in wildlife. This is, of course, an understudied area of wildlife health, but even within zoological medicine, cancers are often not cited as a major/highly prevalent concern for many species. For example, Fowler’s Zoo and Wildlife Medicine, a key text in zoological medicine, cites only DFTD among key noninfectious diseases of marsupials, with no other neoplastic disorders mentioned. Further, Vittecoq et al 2013 TREE point out that “the incidence of cancers in wildlife is poorly understood.” Again, I feel that DFTD is a better model for infectious disease-induced behavioral change, especially given the uncertainty of the actual prevalence of

neoplasias in wildlife. The current strong emphasis on the importance of cancers in wildlife requires much more discussion/support in the introduction, in particular.

Response 3 - We have altered our statement in the Introduction (line 87) by adding "The incidence of cancers in wildlife is poorly understood,…" and referencing the suggested paper by Vittecoq et al. (2013). Additional changes made in response to the earlier comment regarding the focus on cancers have also contributed towards addressing this comment.

Comment 4 - p. 8- Could you talk a little bit more about how and why you settled on a 14-day period for the analysis of network metrics? Is there a biological motivation for this period? How sensitive are these node-level metrics to different periods of aggregation?

Response 4 - The 14-day time period represents the time over which we were realistically able to pick up new infections (clinical symptoms), while also allowing a fine scale enough time period to pick up any shifts within seasons. It also allowed for more time windows in each state (DFTD – or +) for each individual that shifted between healthy and diseased, allowing for a more robust model than could be achieved using longer time periods. We have added a sentence in the Methods (line 171) stating: "The 14-day period represents enough time to identify new infections (clinical symptoms of DFTD), whilst being sufficiently temporally fine-scale to identify shifts within seasons."

Comment 5 - Lastly, per the journal guidelines "It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository." The authors have stated that they will upload data to a Dryad repository, but right now it is not possible to verify the analyses or results for this manuscript. I would encourage the authors to make sure that code is reproducible and publically available to support this manuscript.

Response 5 - We have uploaded our data and code to a Dryad repository under the link – https://doi.org/10.5061/dryad.xksn02vdp

Comment 6 - p. 2 (abstract)- what is meant by "knock-on effects"?

Response 6 - Understand that this was not very clear – have changed to "a pattern with repercussions for DFTD transmission"

Comment 7 - p. 3 - The first sentence "Behavioral interactions are influenced…" sets up the reader to expect the paper to focus on the role of proximate and ultimate factors which is not the

case. It may be better to clearly introduce examples of proximate and ultimate causes as they relate to this system or delete this sentence altogether as it does not relate well to the overall objective of the manuscript.

Response 7 - Agree that this is not the main focus of the paper, so have removed the reference to proximate and ultimate factors.

Comment 8 - p. 3, 1st paragraph- in the sentence "Alterations to behaviour can be driven by gradual physiological changes in the host, when they are expected to be contingent on infection stage." What is "they" in the second part of the sentence? Suggest restructuring the sentence for clarity.Maybe "... and are expected to be…"

Response 8 - For clarity, we have amended to "and are expected to be".

Comment 9 - p. 3, 2nd paragraph- is the behavioral response to infection truly as dichotomous as the authors present it? Arguably, healthy individuals may sometimes seek out disease carriers through aggression or predatory behaviors. Perhaps it may be better to frame the dichotomy (i.e.: the two interacting factors of behavioral responses) is based on which individual is the actor: either healthy individuals can be the actor (examples being avoidance behavior or aggression toward infected individuals) or infected individuals can be the actor (examples being isolating from or aggression toward uninfected individuals (rabies))

Response 9 - Reviewers suggestion is good, as it avoids presenting the situation as entirely dichotomous. We have reworded the first two sentences of 2nd paragraph to read – "Behavioural responses to infection can be observed in healthy individuals as well as disease carriers. Healthy individuals may alter their behaviour by avoiding sources of infection, while infected individuals may undergo disease-induced behavioural changes."

Comment 10 - p. 4- 2nd paragraph- Is cancer truly a high morbidity disease in wildlife? The included citations do not seem to specifically support this idea.

Response 10 - Have changed "morbidity" to "mortality"

Comment 11 - p. 4- 2nd paragraph: Using the word "cancer" seems much to broad to be making those claims. Maybe specify some cancer types or say "some forms of cancer/neoplasia". Also, can "virulent" be used to describe cancers that are non-infectious?

Response 11 - Have altered to read "Animals affected by most forms of cancer…" Also removed the reference to high virulence – as noted by the reviewer, this is not a universally appropriate term.

Comment 12 - p. 4- the question of sickness induced behavioral changes on network connectivity and disease transmission has been addressed in theoretical contexts which may be worth addressing/including:

- (White et al., 2018): this study uses TERGMS to simulate disease spread on dynamic networks with sickness induced behavioral changes having important dampening effects on disease spread

Response 12 - Agree that this is worth addressing – have added the sentence (line 69) "While questions of sickness induced behavioural changes have been addressed in a theoretical context [White et al. 2018], the effects of avoidance and sickness behaviours can be difficult to disentangle in populations of wild animals.

Comment 13 - p. 5, 2nd paragraph - "Transmission is driven by the social and aggressive behavior of the species…" It may be useful to link this statement more directly to the occurrence of biting/fighting behavior relevant to transmission and when/how this occurs in devils (and if it is expected to vary seasonally). For example: is there more intra-sex over mates or is biting a part of mating behavior (inter-sex transmission) making transmission more likely during the breeding season? Or is competition over food a common source of bite interactions and therefore transmission probability is high year-round?

Response 13 - These patterns are mentioned later in the manuscript, but are probably worth alluding to earlier. Have added the sentence (line 102) "The majority of transmission is expected to occur during the devils mating season, when both interaction and injury rates peak [Hamilton et al. 2019]."

Comment 14 - p. 5, 2nd paragraph- I think "immunocomprise" needs to be "immunocompromisation" in the following sentence: "The disease severely impacts the health of infected individuals, particularly as tumour volume increases, resulting in immunocompromise, poor body condition and lack of competitiveness in resource acquisition [33]."

Response 14 - Amended to "compromised immune function" for clarity.

Comment 15 - p. 6, first paragraph - The use of 'switching' as the verb in the sentence "We used a series of network autocorrelation models…" is a strange choice. Perhaps something with more biological relevance such as 'converting' or even 'becoming infected' ?

Response 15 - This sentence has been removed from the manuscript along with the NAM analysis.

Comment 16 - p. 7 last sentence- I would use colon rather than a hyphen to introduce the equation for tumor volume.

Response 16 - Amended as suggested.

Comment 17 - p. 8, 2nd paragraph- why the choice to weight edges by frequency of contacts versus the duration of contacts? Is there a biologically/transmission relevant justification for this choice?

Response 17 - In previously studied Tasmanian devil networks in Hamede et al. (2009) and Hamilton et al. (2019), networks constructed based on frequency and duration of contacts were found to be structurally identical in devils, with no observed divergences in network metrics between individuals. Our methodology is consistent with previous research, as it encapsulates two important aspects of devil interactions (qualitative and quantitative). Additionally in the TERGM analysis the networks are binary, so there would be no distinction between frequency and transmission-based networks. Have added a sentence in Line 177 indicating that frequency is used in order to maintain consistency with previous research – "(consistent with previous research into devil networks [30, 35])"

Comment 18 - p. 8 last paragraph- for clarity, it would be best to specify that weighted degree is not just the number of individuals associated with a particular node, but that it is modulated by the relative strength of those interactions.

Response 18 - Have clarified in line 178: "i.e. edges represent the relative frequency of interactions between each pair of nodes."

Comment 19 - p. 8 last paragraph - In addition, it would be more clear to refer to the metrics mentioned here (namely "total of number of interactions" and "weighted degree") using the same words later in the text (i.e. chose and be consistent with either "total number of interactions" or "interaction frequency" and either "weighted degree" or "degree"). These are mentioned later in the text using different wording: on p.11 second paragraph ("Interaction frequency differed significantly…" and "Degree was significantly lower in DFTD…" and p.14 Fig 2 legend ("a) interaction frequency b) degree…").

Response 19 - Amended to "degree" in 2 instances (line 183 & line 229). Amended to "interaction frequency" in line 189 and in legend for Figure 1.

Comment 20 - p. 8 last paragraph-- I wonder are the definitions for betweenness and closeness clear enough for an audience not so savvy with contact networks. Adding the biological relevance of these network metrics could also be useful to clarify what makes betweenness and closeness centrality different in the context of devil social networks and why these could be important in DFTD transmission.

Response 20 - A very good suggestion. Have amended the description for both measures, so that betweenness (line 184) now reads: "the number of shortest paths flowing through an individual; a measure of their importance in connecting disparate parts of a network", while closeness centrality (line 185) now reads: "sum of all shortest paths flowing through an individual; highlights nodes best placed to influence the entire network most quickly".

Comment 21 - p. 9 first paragraph- What do you mean by "nodes shuffled by disease status"? It's a little unclear whether it's the status of the nodes or the edges between nodes that are being randomized.

Response 21 - Have altered sentence in line 190 to read: "… these were compared to 10,000 randomised networks that had the disease status of each node allocated at random". Hopefully this clarifies that node status, as opposed to edges, are being shuffled.

Comment 22 - p. 10- unlike the other network terms, clustering coefficient has not yet been defined.

Response 22 - We have removed clustering coefficient from the analysis having assessed that it's not really a metric relevant to DFTD transmission. It measures the tendency for clusters of closely connected individuals to form within a network – this isn't an observed tendency of devils in previous studies, and doesn't have any direct relation to DFTD transmission potential.

Comment 23 - p. 10- could you please clarify what you mean by "all network terms were centred"- do you mean that all the values were normalized?

Response 23 - This sentence has been removed along with the NAM analysis.

Comment 24 - p. 10- consider adding an additional sentence about what the weightlag() term is and how it accounts for network non-independence.The interpretation of the weightlag() term in the results section (p.18, first paragraph) suggests this term indicates the likelihood of individuals to interact with other individuals of the same disease status, but the initial explanation given on p.10 only mentions "the non-independence of connected individuals" and doesn't clarify the nature of this non-independence.

Response 24 - This sentence has been removed along with the NAM analysis.

Comment 25 - p. 11, 2nd paragraph- what are the "f"s in the parenthetical model results? Are these the same as "F"s in Figure 1. Assumed that "f" corresponds to "Fortnight" but this was ever explicitly stated.

Response 25 - Apologies, after a re-read we realised that we had not clarified or standardised this. The "F" has been clarified as relating to "fortnight" in the caption for Figure 1, while all the parenthetical model results in the 2nd paragraph of the Results have been amended to uppercase "F"s to relate directly to Figure 1.

Comment 26 - Figure 1 legend: this is nitpicking, but do you want to say that node size is "scaled" by category of tumor load?

Response 26 - Amended to "… where size is scaled by tumour load category"

Comment 27 - Figure 1 legend: Also unclear what the numbers in parentheses correspond to (e.g. 1= 0.0001-50 cm3). Does "1" mean 100% bigger?

Response 27 - Tumour load categories (1 to 4) scale up in 50cm^3 increments, based on those used in a DFTD modelling paper by Wells et al. (2017). The numbers purely refer to categories, and have no specific relation to the % tumour load has scaled up by. These categories are also mentioned in the Methods section in line 171 ("Tumour load on each individual at each timestep was categorised into four levels (as per [31]); (1) 0.0001 – 50 cm3, (2) > 50 – 100 cm3, (3) > 100 – 200 cm3 and (4) > 200 cm3."

Comment 28 - Figure 1 legend: It would also make sense to share any scaling that has been done to depict edge weight or explicitly state if no scaling has been performed.

Response 28 - Scaling has been performed to be (dyad interaction frequency/30) – this was necessary to ensure that edge weights numbering in the hundreds could be depicted without obscuring large parts of the network. We have added the sentence "Edges have been scaled to represent (dyad interaction frequency/30), to allow depiction of high edge weights without occluding entire networks."

Comment 29 - Figure 1 legend: Could you go ahead and remind the reader which fortnightly contact networks (F1-F12) correspond to mating vs. non-mating season?

Response 29 - We have amended Figure 1 to highlight networks corresponding to the devils mating season.

Comment 30 - Figure 2: please add asterisks above significant differences. It is often difficult to see if CI bars are overlapping.

Response 30 - We have added asterisks in Figure 2 corresponding to significant differences between healthy and DFTD-infected individuals.

Comment 31 - p.16 The way the TERGMs were introduced on p.9 ("...used to investigate whether individual interaction patterns within a contact network differ as a result of infection status, tumor load, or number of bite wounds accrued…") implies that parallel analyses would be run for each of three factors (DFTD status, tumor load, and number of wounds). However, when the results are presented on p.16, the probability of edge formation with respect to DFTD infection and tumor load are discussed, but not with respect to bite wounds. Bite wounds is instead included as a model term in both the models of DFTD status and tumor load (p.17 Table 1). There is a disconnect in how bite wounds are modeled between the methods presented on p.9 (bite wounds are presented as a factor on the same level as DFTD status and tumor load, influential in predicting edge formation) and the results presented on p.16 (bite wounds as a factor in the model (like 'sex' or 'memory') of the influence of DFTD status and tumor load in predicting edge formation). Clearer language about inputs and outputs would be helpful.

Response 31 - Thank you for this observation. We have amended the paragraphs covering TERGMs to present "Wounds" as a covariate in each model, as opposed to a distinct avenue of investigation as insinuated previously. A section reading – "nodefactor/cov (Wounds) – the number of bite wounds (discrete numerical covariate) accrued over the time periods modelled, effectively a

proxy of infection risk in the devil/DFTD system [29].” has been added where the model terms are introduced in the 2nd paragraph of the TERGMs section. This brings the inputs into line with the outputs.

Comment 32 - p. 17 1st paragraph- just to clarify, by “sex-mixing” you are referring to propensity to mix with same or different sex (i.e. homophily) in Table 1?

Response 32 - We have now clarified this within the sentence, so it now reads “… while sex-mixing was unbiased towards either homophily or heterophily through time in both seasons”

Comment 33 - p. 18, 1st sentence - For clarity, I would suggest “network metrics examined by season” as opposed to “seasonal network metrics”

Response 33 - Have removed this section of the Results along with the NAM analysis.

Comment 34 - p. 18, 1st sentence- I think “devil’s” should be “ devils’ ” as you are referring to predictors for all devils.

Response 34 - We have removed this section of the Results along with the NAM analysis.

Comment 35 - p. 19- I think the conclusion that “the network position of healthy animals had no clear influence on their likelihood of developing clinical signs of DFTD in the short-term.” could use some additional context with existing literature. This is a question that has been investigated fairly extensively in wildlife to date. For example:

o (Corner et al., 2003): for brushtail possums experimentally infected with bTB, animals that naturally contracted bTB from experimentally infected individuals were more likely to be central to the network. Specifically, they had higher closeness and flow-betweenness scores relative to individuals that did not become infected naturally.

- (Drewe, 2010): meerkats more central to the network were not de facto more likely to be infected with bTB

Response 35 - We have removed this section of the Results along with the NAM analysis.

Comment 36 - p. 20- in the sentence, “[...] particularly at high tumour volumes, indicates a threshold beyond which the effect of cancer on behaviour becomes pronounced.” This is an example where the authors have overgeneralized “cancer,” as not all cancers are associated with tumor volume, per se (e.g. blood cancers).

Response 36 - We have amended “cancer” to “disease burden” in this sentence.

Comment 37 - p 20 2nd paragraph: Is body condition being used as evidence of decreased competitive ability/is body condition linked to behavior in this comparison? That would be a hard factor to isolate from cancer cachexia.

Response 37 - Mating interactions in devils are very physical, so if one participant is in extremely poor condition (either from the accrued effects of previous mating interactions, OR from the effects of DFTD) they are unlikely to secure a mating interaction in the first place. Our point was that at the end of the mating season healthy animals have been involved in multiple mating interactions (both male and female devils can mate multiple times, with different individuals), so are in poor condition (animals don't eat for days to weeks at a time while mating). This presents an opportunity for animals in poor condition, as a result of DFTD infection, to be physically competitive enough to secure a mating interaction. We are not attempting to isolate condition loss from anything specific, merely hypothesise why DFTD-infected animals appear to procure mating interactions late in the mating season, but not early on. The effect of mating season (with severe reductions in immunocompetence and loss of condition) in dasyurids is well studied, and we have provided references to some of this research in the text (McDonald et al. 1986; Dickman & Braithwaite 1992)

Comment 38 - p 20 end of 2nd paragraph-- Are DFTD (+) individuals infrequently interacting or just less frequently than others? This has an impact on your assertion in the next paragraph

Response 38 - A bit of both, but definitely less frequently than healthy individuals (see Fig 2a). We have altered our phrasing to "relatively infrequently"

Comment 39 - p. 20- why are individuals expected to be most likely to transmit DFTD when tumours are at their largest? Can you cite or explain this reasoning more?

Response 39 - We have added a citation to Obendorf & McGlashan (2008) to support this expectation. While there is no definitive evidence of this (it is, at the moment, impossible to precisely identify specific transmission events as there is no pre-clinical test for DFTD), it is a matter of probability. Devils with large tumour loads in and around their oral cavity would be expected to be more likely to transfer tumour cells to an aggressive interaction partner, purely because there is a greater tumour surface area for the other individual to come into contact with. We have also amended the sentence in question (line 376) to read – "Individuals are expected to be most likely to transmit DFTD to new hosts when tumours are at their largest ***because of the greater area of infected tissue***" for clarity.

Comment 40 - p 21 in sentence "Secondly, if any avoidance behaviour occurs in healthy animals, their poor condition and requirement for sustenance may now outweigh the potential costs of interacting with an infected individual"-- Why would an individuals poor condition and hunger make it more likely to interact/stop avoiding sick individuals? Less energy to fend them off or be choosy with a mate? Would they not be just searching for food solitarily? I may not know enough about devils. Also wondering how this leads into the next sentence "Thus there is….". I would like to see references to your data supporting this. Overall, while the analysis on p.21 presents an interesting and potentially important implication of DFTD transmission revealed by this study, the arguments presented lack clarity. More clear wording should be used to identify if the authors are referring to interactions between infected and healthy individuals via competition for mates or food resources

(or both). While both of these may occur and be important for transmission, the argument as written blends these two drivers of interactions in a way that confuses and weakens the argument.

Response 40 - We agree that some of the arguments made here were somewhat speculative, and took away from the main point – the implication for transmission dynamics of late season interactions involving DFTD-infected individuals. We have removed the section of 5 sentences from "Healthy male devils have already likely been involved" to "[….] may now outweigh the potential costs of interacting with an infected individual", which focuses the argument and removes the speculation on cause.

Comment 41 - p. 21- I'm not sure the results shown in figure 2 really support the conclusion that late-season interactions would be "critical." The differences shown in figure 2 don't exhibit a particularly strong/consistent pattern, especially for calling the effect "critical" (depending on the network metric considered, DFTD and healthy individuals overlap for 1 or 2/5 to 5/5 fortnightly timesteps during the mating season).

Response 41 - We have changed the sentence in question to read: "While aggressive mating season interactions have been identified as key to DFTD spread previously [29, 30], our results indicate that late-season interactions may be particularly important sources of transmission events."

Comment 42 - p. 22- capitalize "dasyurids" if referring to taxonomic family?

Response 42 - Dasyurid is a term stemming from the marsupial family Dasyuridae (the marsupial carnivores). It is generally written without capitalisation, in a similar fashion to rodent (from Rodentia) or canid (from Canidae).

Comment 43 - p. 22- it seems that GPS and/or accelerometer data would have been helpful to try to detect evidence of avoidance behavior or changes in activity levels. I'm not proposing that more data need be collected for this study, but this could be a useful future direction to mention/limitation of the current study.

Response 43 - Absolutely, this is a very interesting future avenue of research that we'll hopefully be able to conduct soon. At the time of the study, combining proximity logger & GPS technologies was logistically difficult, but these challenges are being overcome. We have added a sentence at the end of this paragraph noting: "Future studies combining interaction data with geographical location will be useful to investigate avoidance behaviour further."

Comment 44 - p. 22, 2nd paragraph- the references supporting sex-specific differences in infection and cancer costs/survival seem to be quite limited, especially given the extremely broad scope of this statement.

Response 44 - We have altered the sentence to read "There is growing evidence that effects of infection can be sex-specific, whereby the sexes bear differing costs of infection [47, 48, 49] and varying abilities to combat or survive aggressive diseases like cancer [50, 51]. We have also added the following references to support the initial statement:

- Xiao J, Kannan G, Jones-Brando L, Brannock C, Krasnova IN, Cadet JL, Pletnikov M, Yolken RH. 2012 Sex-specific changes in gene expression and behavior induced by chronic *Toxoplasma* infection in mice. *Neuroscience* **206**, 39-48.

- Teffer AK, Hinch S, Miller K, Jeffries K, Patterson D, Cooke S, Farrell A, Kaukinen KH, Li S, Juanes F. 2019 Cumulative Effects of Thermal and Fisheries Stressors Reveal Sex-Specific Effects of Infection Development and Early Mortality of Adult Coho Salmon. *Physiol. Biochem. Zool.* **92(5)**, 505-529.

Comment 45 - p22- Was it only one F-F pair that remained together after one became infected?

Response 45 - There was one female-female pair in which the social bond remained after one female became symptomatic. We have clarified this in the wording of paragraph 4 in the Discussion, focusing it to talk about this specific example. We thought it was an observation worth noting due to the clear evidence of the strong dyad persisting in spite of DFTD infection, which is of interest in the discussion of avoidance behaviour.

Comment 46 - p. 23- another interesting study to discuss in the context of behavioral avoidance might be: (Croft et al., 2011): explored how groups of fish reacted to the introduction of either an infected or uninfected individual. They found that infected guppies associated less with the group than their uninfected counterparts.

Response 46 - Thank you for highlighting this study – we have included a refernce to it in the Introduction (line 72).

Comment 47 - p. 23, concluding paragraph- “It is considered [...]” consider rewording for more strong/active phrasing. Additionally, this sentence should go in the introduction, rather than the final paragraph, to support the highly unusual case of DFTD as a model of cancers in other species. Even with moving this sentence, however, I still feel that DFTD is a poor model of cancer-induced behavioral change in the extremely broad context the authors have used throughout.

Response 47 - We have altered the final paragraph to read: “Evaluating the effects of disease on behaviour is rare in wildlife studies, owing to the difficulty of diagnosis and following disease progression in a wild setting. Here we provide evidence that progression of a transmissible cancer alters interaction rates and position within a social network in Tasmanian devils. This has implications for our understanding of how infectious cancers may evolve and spread. Fifteen to twenty percent of cancers in humans [58], possibly even more in wildlife [59], have been associated with direct infectious origins. Improved knowledge of the behavioural side-effects of infectious diseases can help to further understand their overall ecological and evolutionary effects in wildlife across a broad range of taxa.”

Reviewer 2

Comment 1 - 1) Introduction, first sentence: “Behavioural interactions are influenced…” you mean Behavioural interactions between individuals ? species ? please precise.

Response 1 - We have amended this sentence to read “Behavioural interactions between individuals are influenced…”

Comment 2 - 2) Introduction, at the end of the first paragraph, maybe authors could also cite this reference:

Ezenwa VO, Archie EA, Craft ME, Hawley DM, Martin LB, Moore J, White L. 2016 Host behaviour-parasite feedback: An essential link between animal behaviour and disease ecology. Proc. R. Soc. B Biol. Sci. (doi:10.1098/rspb.2015.3078)

Response 2 - Thank you for the suggestion – we have included the suggested reference.

Comment 3 - Introduction, the first sentence of the second paragraph.

The sentence “Behavioural responses to infection are the result of two interacting factors – avoidance of disease carriers by healthy individuals and disease-induced changes in behaviour of infected individuals.” Should be:

The sentence “Behavioural responses to infection are the result of AT LEAST two interacting factors – avoidance of disease carriers by healthy individuals and disease-induced changes in behaviour of infected individuals (Moore 2002).”

Indeed, there is a HUGE literature on host-manipulation by parasites. There is also self medication phenomena, sometimes self sacrifice, see (4). I understand that this is not the direct topic of your study, but you cannot in opinion reduce your statement like that, as it is a bit naïve and/or it suggests that you are voluntarily ignoring these important phenomena.

Response 3 – The first reviewer had a similar comment with regard to this sentence – it was presented as a dichotomy before, which is not the case. We have rewritten the sentence so that it is clear that we are presenting 2 of the key drivers of behavioural alterations where either infected or unifected individuals are the instigators: “Behavioural responses to infection can be observed in healthy individuals as well as disease carriers. Healthy individuals may alter their behaviour by avoiding sources of infection, while infected individuals may undergo disease-induced behavioural changes”. While host-manipulation is a topic of huge interest, it’s not really within the scope of this paper, where we focus more on the behavioural effects of disease itself.

Comment 4 - 4) Sentence between page 3-4; Sometimes social isolation also permits to prevent the infection of kin related individuals (e.g. self sacrifice, e.g. Shorter JR, Rueppell O. 2012 A review

on self-destructive defense behaviors in social insects. Insectes Soc. (doi:10.1007/s00040-011-0210-x)

Response 4 - Thank you for the suggestion and reference. We have amended the sentence to include avoidance of kin infection and incorporated the suggested reference.

Comment 5 - 5) End of page 4, I am not sure that cancer is always "highly virulent" among animals (even in humans, the more we get old the more we have for instance in situ carcinoma without significant health effect). I would thus change the sentence: "Studying the behavioural effects of oncogenic processes in wild populations is both ecologically and epidemiologically relevant across a broad range of taxa, as cancer is a highly virulent and ubiquitous disease present in most multicellular organisms [25]. By "Given the ubiquity of oncogenic processes in most multicellular organisms [25], studying their behavioural effects in wild populations is both ecologically and epidemiologically relevant across a broad range of taxa."

Response 5 - Agree that the suggested wording makes the focus of the sentence clearer. Have removed the reference to high virulence and reorganised the sentence as suggested.

Comment 6 - 6) Page 21, given that the behavioural changes you observe are apparently 'good' for the cancer transmission, is it possible that the patterns you observe results from a host manipulation by DFTD to favour its transmission ? After all, many parasites develop strategies for their transmission, including the way they induce pathological consequences on the host, if this is good for the transmission...

Response 6 - This is definitely an interesting concept, and one worth discussing in future work. To make an assertion of host manipulation by DFTD we would have to have a more complete picture of tumour genetics within both the individual and the population, which we don't have right at the moment (we will in future though). While it's a bit beyond the scope of this work, it's definitely worth investigating.

Appendix B

Response to Proc B reviewers – Infectious disease & sickness behaviour manuscript

We thank the reviewers and the editor for their constructive reviews of our paper which we feel have improved the manuscript considerably.

The only change requested was that we fix the broken Dryad link, which we have now done. Note that the problem was with the privacy settings on the file upload, so the manuscript itself has not been altered from previously, but the link in the "Data Accessibility" section now works. Apologies for this oversight – we had made the repository accessible to manuscript reviewers initially, but posted the incorrect link in the manuscript. The repository is now fully public, so the original link will now work.

Thank you for the very positive comments and acceptance of our manuscript.