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PROCEEDINGS B

Virulence-mediated infectiousness and activity trade-offs and their impact on transmission potential of influenza patients

Brian McKay, Mark Ebell, Ariella Perry Dale, Ye Shen and Andreas Handel

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Review timeline

Original submission:	27 August 2019
1st revised submission:	2 March 2020
2nd revised submission:	16 April 2020
Final acceptance:	17 April 2020

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

Review History

RSPB-2019-1997.R0 (Original submission)

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?
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.
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
This manuscript investigates the existence of a virulence-transmission tradeoff in influenza. With questionnaire data from flu-infected patients, the authors are able to correlate the severity of symptoms (number of unique, uncorrelated infection symptoms) with with measures of infectiousness (number of unique, uncorrelated symptoms likely to influence transmission) and activity levels (a proxy for contact rates). Since the former relationship is positive while the latter is negative, the inference is that an intermediate level of disease severity should maximize transmission potential. I think this is a neat study and the authors have made the most out of the sort of qualitative (i.e., do you have this symptom? Y/N) data available to them. I agree with the authors that despite a large body of theoretical work and data from experimental model systems, there is very little trade-off hypothesis-supporting data from human diseases. This paper will make a nice contribution to that space. That said, I think a subtle rearrangement of the manuscript might help it fit more neatly into that space.

Main comments.
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Review form: Reviewer 2

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

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Acceptable

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11. Tables 1 + 2 can be moved to the supplement or else the authors should justify the need to include them

Decision letter (RSPB-2019-1997.R0)

24-Oct-2019

Dear Mr McKay:

I am writing to inform you that your manuscript RSPB-2019-1997 entitled "Virulence-mediated infectiousness and activity trade-offs and their impact on transmission potential of patients infected with influenza" 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:
The referee reports are generally positive but identify some important points around the presentation and definitions. I think that the clarity of the paper will be much improved by a thorough rewrite of these sections and I encourage the authors to do that, making sure to address the concerns of the reviewers.

Reviewer(s)' Comments to Author:

Referee: 1

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Author's Response to Decision Letter for (RSPB-2019-1997.R0)

See Appendix A.

RSPB-2020-0496.R0

Review form: Reviewer 1

Recommendation
Accept with minor revision (please list in comments)

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Good

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Decision letter (RSPB-2020-0496.R0)

11-Apr-2020

Dear Mr McKay

I am pleased to inform you that your manuscript RSPB-2020-0496 entitled "Virulence-mediated infectiousness and activity trade-offs and their impact on transmission potential of patients infected with influenza" has been accepted for publication in Proceedings B, pending some final revision.

The referee has recommended publication, but also suggests some minor revisions to your manuscript. Therefore, I invite you to respond to the referee's comments and revise your manuscript. 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.

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
NB. From April 1 2013, peer reviewed articles based on research funded wholly or partly by RCUK must include, if applicable, a statement on how the underlying research materials – such as data, samples or models – can be accessed. This statement should be included in the data accessibility section.

If you wish to submit your data to Dryad (http://datadryad.org/) and have not already done so you can submit your data via this link
http://datadryad.org/submit?journalID=RSPB&manu=(Document not available) which will take you to your unique entry in the Dryad repository. If you have already submitted your data to dryad you can make any necessary revisions to your dataset by following the above link. Please see https://royalsociety.org/journals/ethics-policies/data-sharing-mining/ for more details.

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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

Reviewer(s)' Comments to Author:
Referee: 1

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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.

If you are likely to be away from e-mail contact please let us know. Due to rapid publication and an extremely tight schedule, if comments are not received, we may publish the paper as it stands.

If you have any queries regarding the production of your final article or the publication date please contact procb_proofs@royalsociety.org

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Proceedings B
mailto: proceedingsb@royalsociety.org

Appendix A

We appreciate the useful feedback we received. The following provides a detailed reply to all feedback. Our replies are shown in bold below each point.

Board Member: 1

The referee reports are generally positive but identify some important points around the presentation and definitions. I think that the clarity of the paper will be much improved by a thorough rewrite of these sections and I encourage the authors to do that, making sure to address the concerns of the reviewers.

We appreciate the positive feedback. We have followed the reviewers' suggestions, addressed their concerns as described in detail below, and based on their feedback revised, rewrote and restructured our manuscript.

Referee: 1

This manuscript investigates the existence of a virulence-transmission tradeoff in influenza. With questionnaire data from flu-infected patients, the authors are able to correlate the severity of symptoms (number of unique, uncorrelated infection symptoms) with measures of infectiousness (number of unique, uncorrelated symptoms likely to influence transmission) and activity levels (a proxy for contact rates). Since the former relationship is positive while the latter is negative, the inference is that an intermediate level of disease severity should maximize transmission potential. I think this is a neat study and the authors have made the most out of the sort of qualitative (i.e., do you have this symptom? Y/N) data available to them. I agree with the authors that despite a large body of theoretical work and data from experimental model systems, there is very little trade-off hypothesis-supporting data from human diseases. This paper will make a nice contribution to that space.

We appreciate the positive feedback on our study.

That said, I think a subtle rearrangement of the manuscript might help it fit more neatly into that space.

We have rearranged the manuscript as suggested and as described more below.

Main comments.

1. While I have (lazily) summarized this as being about "virulence-transmission tradeoffs", the title makes clear that the reality is more nuanced than that (a "virulence-mediated" tradeoff). The word "virulence" is doing a lot of work in the intro and abstract, subsuming a bunch of variably-related measures (symptoms, activity levels, morbidity). Some very clear and explicit statements about the use of "virulence" would be welcome here. I wonder, though, if more mileage would be gained from moving some of the text from the "Conceptualizing" section to the intro? This "T ~ p x c x d" formulation helps provide context for the other human infection studies (e.g., for HIV they measure p and d and correlate both with set point viral load; for dengue — a Ben-Shachar & Koelle 2018 study that could also be referenced — they also measure p and d and correlate both (I think) with viral production rates). I see

two nice features of bringing this conceptual framework up front. First, those two papers both focus on d, but different drivers of d ("virulence" in the conventional death (time to AIDS) sense, and clearance, respectively), so the formulation covers a bunch of potential tradeoffs and mechanistic details. Second, it also lays bare that the c variable hasn't had as much scrutiny from data, though has been a major part of verbal and mathematical arguments about pathogen evolution. I think this might avoid some unnecessary woolliness in the introduction. (But, I might be wrong.)

We have followed this suggestion and restructured the text such that parts of what used to be in the 'Conceptualization' section are now in the introduction. We now refer to the conceptual figure in the intro. We also moved the text explaining that figure to the introduction, updated references as suggested and ensured we are as clear as possible about terminology (virulence/morbidity/etc.).

2. line 61-63. This statement was a surprise to me, since I thought Mackinnon & Read 2004 Virulence in malaria: an evolutionary viewpoint. Proc B. presented human malaria data that WAS consistent with the tradeoff hypothesis (their Figures 5 and 6; text at the bottom left of p. 972). I think some of the same data is presented in the 2008 paper referenced here, so I'm not sure what I'm missing…

While Mackinnon et al in both their 2004 and 2008 papers suggest that the *human* malaria data is consistent with the trade-off hypothesis (and we do not dispute this), the data do not suggest a trade-off *as mediated through increased per-contact transmission potential and reduced infectiousness duration*. Instead, reduced transmission fitness at high virulence is assumed to be mediated by host death. For the data shown in the 2004 paper, increased virulence seems to increase fitness with no trade-off noticeable within the range of what the data covers (their fig 6a). We rewrote these sentences to be clearer.

3. l. 180-181. It seems that none of the main inferences are changed in the supplementary analysis, is that right? Either way, a line about inferences from the supplementary analyses would be nice to have in the results. Similarly, the curved relationship that cannot be explained in line 202 goes away with the inclusion of the empirically-diagnosed cases, right? Useful to mention this here?

Based on comments from the second reviewer, we have made adjustments to the way we compute the score. We now have one way to compute the scores in the main text, and show several alternative approaches in the SM. We also show the analysis for all influenza diagnosed cases in the SM. We have a section in the main text where we briefly summarize results from our sensitivity analyses (not much changes) and provide details in the SM.

4. The choice of "limitations" to discuss seems funny to me. It's not clear why the type or sub-type would matter. There might be quantitative differences, but given similar pathophysiology and the coarse scale of the data would we expect observable variation? On the other hand, I would love to read more discussion of the extent to which this measure of "per contact transmission potential" reflects 'true' infectiousness? What is known about infectious dose in influenza, and how much variation is there in virions per aerosol droplet (or whatever) across hosts?

We have significantly revised the discussion section to address these points.

5. This might be too far outside the box, but fever caught my attention as a symptom that might actually be recovery- rather than morbidity-related. Ref 57 talks about the adaptive value of fever in its intro (i.e., immunity operates more effectively at higher temperatures) and cites some studies showing that treating fevers prolongs symptoms. I suppose with only one symptom there is no chance of investigating correlations between "recovery" and infectiousness, and presumably leaving fever out of morbidity measures wouldn't change anything. Though, the fact that I got distracted by fever does highlight the challenge of neatly categorizing symptoms. Perhaps this too could have more discussion? (Relatedly, around line 170 it wasn't clear to me how "chest congestion" could plausibly increase infectiousness if it had not been associated with coughing or sneezing.)

We do agree that fever might be related to the infectious period and that it would be interesting to investigate this. Unfortunately, our data do not allow us to explore this further. This will thus have to wait for a follow-up study that includes more detailed data.

We completely agree with the reviewer regarding the overall challenge of – somewhat arbitrarily – assigning symptoms to one or the other category. We discuss this now in some more detail.

It is true that chest congestion alone without coughing or sneezing might not lead to increased infectiousness (though some recent studies suggest that breathing alone accounts for a large fraction of expelled influenza virions). However, it is not unreasonable to assume that chest congestion might be a proxy for pathogen load, i.e. more congestion could indicate higher levels of pathogen, thus potentially correlating with infectiousness. Since we submitted our paper, we have become aware of a recent article (McCoul et al 2019, see full reference in paper) which suggests that "congestion" as reported by patients is very vague and thus might not be a very informative variable. In our revised version, we compute the scores in multiple ways in the SM, some of these analyses include chest congestions, others do not. Our results stay consistent.

6. I like Figure 5. I assume that since the measures are "re-scaled" it is not of much value to also calculate and plot transmission potential?

We don't think the way we measure the quantities p and c would make it meaningful to multiply them to compute some version of the transmission potential since the weighting of each measured quantity and relation to the conceptual quantity is unclear. Further, as we now point out more explicitly, what we are plotting is only the "p and c" component of the transmission potential since we don't have data on the duration of infectiousness part. Thus, we can't say much about the "complete" transmission potential (p*c*d) anyway.

Minor edits.

- l. 77-78. Does "sick/healthy" here mean "infected/uninfected" or "symptomatic/asymptomatic"?

This is referred to as "well" and "unwell" in the original article. So there is no direct measure of infection just the presence (symptoms) or absence (no symptoms) of disease. We have clarified this.

- l. 127. simular -> similar

Fixed

- l. 165-169. Is this text necessary since it's made clear in the methods?

Some journals banish methods to the back of the article (at times in tiny print). We thought this was important for the reader to be exposed to, thus had it in the results section. Fortunately, PRSB is reasonable about the way they format articles, we thus removed some of the overlapping wording from the results section.

- The references have some wonky capitalization of journal titles.

We corrected this.

SM

- l. 195 should this say “empirically diagnosed”?

- l. 208 were -> where

- l. 210 no “were” in “none were had a correlation”; also, later that same line were -> where

- l. 250 no “were” in “main text where were”

Thanks, we fixed all those typos.

Referee: 2

Comments to the Author(s)

The premise of this study is of high interest to the field of epidemiology, however there are some major and minor areas that need to be addressed prior to the manuscript being ready for publication.

We appreciate the reviewers’ overall positive comments. In this revision, we have aimed to address all the concerns that were raised (within the limits of the data we have available). We hope this has lead to a manuscript that the reviewer now finds acceptable.

Major revisions:

1. The infectiousness score. The authors define an "infectiousness score" by (I believe, though it isn't 100% clear) summing the number of symptoms a patient is experiencing with 0 being experiences no symptoms and 4 being experiences all infectiousness-related symptoms. However, this assumes that there can be no compensation. Thus, a person who experiences only 2 symptoms is less infectious than a person who experiences 3 symptoms, but this fails to account for the severity of the symptoms. Perhaps the person with 2 symptoms has them more severe than the person with 3 symptoms and therefore more infectious.

Our scores are indeed computed by counting the number of symptoms which are present. The reviewer raises an interesting point regarding potential trade-offs between number and severity of symptoms. If those were negatively correlated, i.e. if there was some type of compensation between quantity and quality of symptoms, our score creation would be questionable. Since our study analyzes data that was not specifically collected to address our question, we do not have ideal data (e.g. severity for each symptom). Most of the symptoms were reported as absent or present. We do

however have severity levels (on a scale from 0-3) for 3 symptoms, one that is part of the infectiousness score and 2 that are part of the morbidity score. The reviewer's comment led us to investigate correlations between severity of these symptoms and total number of symptoms, i.e. our scores. This analysis is presented in the SM of the revised MS. We do not find evidence for compensation, instead there is a positive correlation between severity and number of symptoms. In our opinion, this makes our use of presence/absence counts a defensible approximation. We still acknowledge that a more detailed score that factored in severity would be better, unfortunately our data does not provide that information.

2. This concern is particularly borne out where the authors state a curved relationship between activity and infectiousness that "[the authors] cannot think of a biological mechanism that might lead to this pattern". Without addressing the issues with their infectiousness score, I would be hesitant to proceed with the inclusion of this score in the manuscript without addressing this fundamental problem.

Based on this feedback, we decided to perform more extensive sensitivity analyses of our results and to compute the infectiousness score several different ways. These additional analyses are shown in the SM and briefly discussed in the main text. Overall, results stay the same. We believe this increases the plausibility that our scores, and results based on them, are meaningful, albeit admittedly limited by the data we have available. Of course, we acknowledge, and explicitly point out in the discussion, that our data is not ideal and as such our study should be considered exploratory and further, more definite studies would be useful.

3. There is bias in only including students in a health-care facility that I don't see the authors mention. The authors state that their population is on the middle of the virulence spectrum based on their assumption that students going to the clinic aren't sick enough to seek treatment but not so sick as to require hospitalization. I would be hesitant to make this assumption without at least exploring this assertion more rigorously because: 1) This is the first time many students have fallen ill away from home and may go to the clinic with relatively minor symptoms and 2) student medical insurance may prioritize the clinic over the hospital (the clinic may not require a co-pay) and thus students may be more sick than expected.

In our experience working with our university's health center, we know that students who are very ill often just show up and, if needed, are transferred to a local hospital. Such students would not fill out the online registration form and thus not be part of our sample. We also know that many students have a co-pay which is similar to that if they sought health care at a doctor's office. This payment, and more importantly the time commitment, likely prevents students from seeking care for very minor symptoms. Thus, we think the 'middle virulence' idea is plausible, while fully acknowledging that it is an assumption we make that we cannot test further. We have reworded our text to be clear that this 'middle virulence' idea is an assumption we make. Any results presented and also do not depend on this assumption.

4. The authors state that "there is no meaningful relationship between infectiousness score and activity level" which could be true or it could be that the infectiousness score is not capturing true infectiousness and this problem is concerning for the underlying results of the manuscript.

We certainly agree that – as in all studies – our results are contingent on the specific data we have and the assumptions we make in analyzing it, especially with regard to the score building. We hope that with our additional sensitivity analyses added to this revision, where we show that results remain robust as we change the data and the way we build the scores, together with some more explicit and detailed discussion of the limitations of our study will convince readers that the result we find might be robust but that at the same time, our findings are exploratory and need to be confirmed in further studies.

5. The authors selected 0.9 as a cut off point and for a sensitivity analysis without describing why they chose these numbers. Yule's Q score ranges from -1 to 1 and thus choosing 0.9 is selecting highly correlated redundant symptoms. The authors provide no insight into why they chose 0.9/0.75 and not 0.5 or 0. Provide justification for this decision

Unfortunately, for better or for worse, the field currently does not have a commonly used Q value (akin to p=0.05) to determine exclusion of colinear variables. For this revision, we decided to not remove any variables based on Q in the main text. In the SM, we show results for 0.9 and 0.75 cut-off. We acknowledge explicitly that these are chosen by us. Results for any of these ways of computing the scores are similar.

6. Lines 246-251. Basically just restates the hypothesis as results without what I feel is appropriate evidence. Please support this assertion better.

We rewrote this section to be clearer about the hypothesis, what our data show, and what that might mean.

Minor revisions:

1. Line 33. "This trade-off determines the transmission potential" I understand this is the premise of the manuscript however this is a very strong statement, there is nothing else that could possibly determine the transmission potential? If there are no other possibilities, can the authors provide proof this is the only possibility?

We agree that our statement was too strong. We rewrote the abstract such that hopefully it is now clear what our study can and cannot show, i.e. that our findings are exploratory and limited to the data at hand, thus needing further investigation and validation.

2. Line 55. Extra comma after "While"

Fixed

3. Line 68. Should at least mention that there is indirect evidence of the relationship between virulence and transmissibility and cite the body of work that indirectly supports your hypothesis

We added references to studies suggesting such trade-offs for other human diseases.

4. Lines 166-167. "To prevent circular reasoning..." This is stated already almost in the same words

We removed one of the statements.

5. Line 177. What do the authors mean by "balanced"?

By that we mean a variable that has values as evenly distributed as possible (in our case as close to 50% Yes and No). We apologize for not being clear about this and state it now explicitly.

6. Line 1182-184. This is confusing. You have already stated you aren't including the symptoms that are redundant this makes it read as if suddenly you are including the.

We edited this paragraph and all other methods and results sections dealing with the score creation to be very clear what is included and excluded in the new way we compute the scores.

7. Line 263. "Individuals with low virulence infections" insert 'or severe infections'

Added

8. Line 271-272. This has been shown in Earn et. al (cited elsewhere in this paper) but you should cite the manuscript rather than just assert this.

We added the suggested citation.

9. Figures 2 and 3 (and maybe 4) can be condensed, either as Figure 1a + Figure 2 and Figure 1b + Figure 3 or Figure 2 + Figure 3 + Figure 4

We followed the suggestion and combined figures 2-4

10. Figure 5 is very difficult to read with overlapping circles and squares. It hides the fact that the infectiousness score is meaningless/wrong/uninformative. This relationship should be made more clear especially if the authors choose not to re-visit their infectiousness score.

We changed the figure somewhat by adding a level of shading and transparency/color to the symbols. We also re-visited the infectiousness score as described above.

11. Tables 1 + 2 can be moved to the supplement or else the authors should justify the need to include them

We agree and moved those to the supplement and now just mention the main findings in the text and refer to the SM.

Appendix B

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".

DONE

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.

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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].

DONE

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

DONE

The relationship between pathogen virulence and transmission potential has been studied extensively theoretically. Our study contributes empirical evidence for influenza infections in humans. We show that among patients with influenza infections, an increase in virulence

(morbidity score) lead to a decrease in activity score and increase in infectiousness score. Our results can help inform current and future interventions as well as future mathematical models.

5) Data accessibility section and data citation
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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

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s).
This is a revised version of a manuscript I have previously reviewed. The authors have provided thoughtful responses to my original comments. I think the edits to the introduction and discussion, especially, help to provide more context for this study.

I think the language is pretty clear in the intro, however I'm still stumbling over the first few sentences in the abstract. E.g., here it says that "virulence induces transmission-enhancing symptoms" and that "virulence can cause host morbidity" while the intro suggests that virulence IS the symptoms. I'm sorry for belabouring the semantics here, but I'm imagining (hoping to) give this paper to undergraduate students in the future and this language will undoubtedly confuse them. If you want to define virulence as symptoms then maybe do this in the abstract too. Perhaps something like "Communicable diseases can be characterized by the severity of the symptoms (i.e., virulence) they induce. While some symptoms may be transmission-enhancing, symptoms contributing to host morbidity can actually reduce overall transmission potential."

The first two sentences of the abstract have been changed.

l. 55-60. I don't think "malaria" should be capitalized. I'd also clarify in line 55-56 "as malaria parasite density increased within a host"

Fixed the capitalization and added the within host statement.

Somewhere around l. 143 I wanted to see all of the symptoms, and their categorization, detailed. This happens in the results, but why not put it in the Methods? Or add a table with columns for infectiousness and morbidity symptoms?

Added Column to SM Table 1 indicating if it was considered infectious or morbidity

I feel like l. 241 could use a bit more detail about the “different ways” scores were computed.

The full details of the sensitivity analysis are provided in the SM and we did not add any text to the main doc.

l. 263-265. I’d be surprised if this were true (and yes, I know that my previous review suggested that this "variable hasn't had much scrutiny"). My intuition is that something about contact rates and transmission potential must exist for HIV. A quick search led me to Cassels et al. 2008 JAIDS 47(S1): S34-S39. There may be relevant references in their section on “Contact Rate”. Alternatively, a slightly tempered statement may do the trick here.

We just removed the sentence.