Author's response to reviews

Title: Quarantine for pandemic influenza control at borders in small island nations

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Author's response to reviews: see over
I am pleased to enclose our revised contribution: Quarantine for pandemic influenza control at borders in small island nations (MS: 1185636897216413).

Revisions were made following the reviewers’ suggestions; point-by-point responses are provided in this enclosure. Revisions are highlighted in red font in the main text.

We hereby approve of the revised manuscript and declare that the manuscript has not been considered for publication elsewhere. We also declare that we have no conflicts of interest. We hope the revised manuscript is now suitable for publication.

Yours sincerely,

Nick Wilson

[--------Responses to the Reviewers--------]

MS: 1185636897216413

1. The authors assumed (p. 7) a combined reproduction number of 3 (2+1) as "the average numbers of symptomatic and asymptomatic secondary transmissions caused by single primary case" and cited references [24] and [25]. I don't see where this number is used in this work. Moreover, this number is larger than the range of reproduction number used in reference [24]. Reference [25] did give ranges of ranges 1.2-3.0 and 2.1-7.5 for community-based and confined settings, respectively. Is it due to the authors' hypothetical setting of a small island nation? The authors should clarify how their assumption is made and how it is used in their work.
Our response: We apologize for the confusion. Our distinction between symptomatic and asymptomatic cases follows that of reference [24]. Using the probability of symptomatic infection, alpha, the basic reproduction number, R_0 is given by (alpha*R_s + (1-alpha)*R_a). Thus, R_s = 2.0, R_a = 1.0 and alpha = 0.67 lead to R_0 = 1.67 which gives a close estimate to [24] and is within the range in [25]. We rewrote the relevant descriptions in the Methods (P7L133-138).

2. The authors used arrival time as the latest time of possible infection but admitted that, "in reality, earlier acquisition of infection would increase the probability of non-infection after quarantine and therefore increase the effectiveness" (p. 8). This affects the result significantly, as time since infection upon arrival is important information but is not considered, leading to perhaps considerable overestimate in optimal quarantine time.

Our response: We agree that the time of infection among infected individuals influences the optimal length of quarantine (P6L102-103). We made the following revisions accordingly:
(1) We have dealt with this issue further in the new Appendix. We employed additional infection-age structured arguments and documented the resulting insights in the Appendix (P25L567-P27L615). The model suggests that the incorporation of earlier exposure to infection requires prior knowledge on the distribution of infection-age when quarantine is started.
(2) Nevertheless, the infection event is not directly observable in reality, and it is impractical to address this issue in all settings. Therefore, we aimed to take a conservative approach which required that the worst case assumptions (ie, favouring disease transmission) were made. This point is now discussed in the Discussion section (P22L491-495).

3. Another factor that was not considered is that the measure of effectiveness only considers the risk of introducing infectives to the community. However, during SARS outbreak, even though there was no evidence of asymptomatic infection for SARS, one study (Hsieh et al. 2005) have shown that an indirect benefit of quarantined is that the previous quarantined infectives were detected significantly faster than those who were not, thereby limiting their opportunities to infect other after onset. That is, the mean time from onset of symptoms to diagnosis for the previously quarantined infective (1.20 days) was much shorter than that of those who were not (2.89 days).
Our response: We thank the reviewer for this helpful comment. We agree that the earlier detection of quarantined individuals than non-quarantined individuals may also be the case for influenza. Since incorporation of this aspect requires further assumptions, and because we assume that all incoming travellers are quarantined in the border control setting, we have now at least discussed this in the Discussion section (P21L471-474). The suggested reference is cited as ref [47] in the revised manuscript.

4. The authors claimed (P. 9) that by assuming that the length of generation time among asymptomatic individuals is identical to that among symptomatic cases yields a conservative effectiveness estimate. It seems to me that whether the estimate is conservative or not would depend on whether the generation time length among asymptomatic individuals is longer or shorter than that of symptomatic cases, which is uncertain since the matter depends on two factors: per contact transmission probability (where asymptomatic transmission might be less due to less virus shedding) and contact frequency (where an asymptomatic infect might have more contact). Hence we are only sure of more uncertainty this assumption brings.

Our response: We thank the reviewer for this comment. We agree that the generation time of asymptomatic cases adds uncertainty to the model prediction, because the quantity is unknown and has yet to be clarified. We made the following revisions:
(1) We rewrote the relevant part in the Methods section appropriately (P10L196-199).
(2) We added a sensitivity analysis on this matter in the Appendix. Since the distribution of generation time among asymptomatic individuals is unknown, we examined the sensitivity of point estimates of the effectiveness of quarantine (at 95% and 99% effectiveness) to different ratios of generation times among asymptomatic to symptomatic cases (P27L617-P28L635 and Figures 7A and 7B).

5. During the 2003 SARS outbreak, many affected areas instituted exit border screening at airport also, which would lower the number of symptomatic infected travelers and subsequently lesson the effectiveness of quarantine since the prevalence of incoming travelers, p, would be smaller (see Equation 6 on p. 12). Another related issue is the authors assume one source country. In the case of multiple affected areas, as in the case of SARS, multiple values of p need to be considered in the expression for PPV and NPV, but which should not be difficult to derive but perhaps harder for simulation purposes.

Our response: We agree that it is of practical importance to consider various settings
of the prevalence of infection among travellers. Nevertheless, we note that:
(1) The effectiveness of quarantine is defined by equation (4) in the main text and is independent of p.
(2) The diagnostic performance PPV is highly sensitive to p. Indeed, PPV will be lowered by exit screening. Nevertheless, a small p would help ensure the absence of secondary transmission (Figures 4 and 5), and thus, smaller values of p offer larger ripple benefits of quarantine (e.g. higher chance of extinction). This point is discussed in P19L425-430.
(3) Theoretically, we believe that p is not necessarily assumed as resulting from one source country (though we wrote as it sounds so, so that general readers will follow our arguments). That is, supposing that there are two sources with prevalence p_1 and p_2 with the total numbers of travellers being N_1 and N_2, our p will be the mean, given by (p_1*N_1 + p_2*N_2)/(N_1 + N_2).

Minor Essential Revisions 1. The authors assumed (p. 7, line 124) a flu symptomatic ratio of 66.7% and cited, among several references, reference [12] which, as far as I can see, gave no such estimate.
>> Our response: We apologize for the confusion. Ref 12 was removed from the suggested part to appropriately discuss the relevant issue in P7L124.

2. I am not sure what the authors mean by "At least, we selected this dataset..." (p. 8, line 150).
>> Our response: We rewrote the relevant part accordingly (P8L153-155).

3. P. 17, line 381, the first two commas are unnecessary.
>> Our response: Two commas were removed (P18L397).

Discretionary Revisions 1. As the authors had noted, perfect quarantine was assumed (p. 6), e.g., perfect quarantine, detection of symptoms, and isolation. Recent studies (e.g., Hsieh et al. 2005) on quarantine for 2003 SARS outbreak have shown the above assumption might be too idealistic, if not unrealistic. Perhaps such results could be useful to quantitatively study the uncertainty due to imperfect quarantine, lack of detection, etc.
>> Our response: We thank the reviewer for this comment. As we noted in P6L102-103,
we have added into the new Appendix consideration of suboptimal case detection within quarantine (P29L653-670 and Figure 7D). But further aspects of the efficacy of quarantine (e.g. secondary transmission under quarantine) are beyond the scope of this analysis.

[-------Response to the Reviewer 2-------]
1) The authors seem to assume that a rapid test can be equally effective in detecting the symptomatic and the asymptomatic individuals. But asymptomatic individuals are likely to shed lower titer of the virus. Therefore it should be expected that the sensitivity of a rapid test is lower for the asymptomatic individual.

   >> Our response: We thank the reviewer for this comment. We agree with the intuitive assumption that rapid diagnostic testing will probably have lower sensitivity among asymptomatic individuals compared to symptomatic ones (P11L220-L224). We have now covered this issue in the new Appendix (P28PL636-P29L651 and Figure 7C).

2) The authors do not consider antiviral prophylaxis for those in quarantine, which may add significant value for effectiveness of the quarantine measure.

   >> Our response: We have added some comments on this point to the Discussion (P23L510-518). We have considered this issue in the following:
   (1) Antiviral prophylaxis will lower infectiousness of quarantined individuals.
   (2) Nevertheless, antiviral prophylaxis will also probably lower the probability of symptomatic infection (or at least make symptoms milder) complicating case finding (and probably leading to lower detection rates of symptomatic cases).
   (3) Thus, the effectiveness of quarantine with antiviral prophylaxis is determined by the interplay between lowered infectiousness and lowered detection. We unfortunately do not have any prior information to clarify this complex issue. Nevertheless, these points are now discussed in P23L510-518.
   (4) We note that island countries are generally poor (developing countries) and cannot usually afford to stockpile antivirals.

3) It is practically impossible to separate all individuals in the quarantine facility. For example, the family with small children needs to stay together in a same room. This makes the transmission in the quarantine facility a real issue.

   >> Our response: We thank the reviewer for this comment. We agree that imperfectness
of quarantine should be carefully considered. There are two aspects of imperfectness: (A) symptomatic case detection and (B) isolation.

(A) Imperfect symptomatic case detection is now explicitly discussed in the new Appendix (P29L653-670).

(B) We agree that imperfect isolation is a realistic concern, which however theoretically complicates the modelling approaches greatly and is out of the scope of the present study. If the unit of group quarantine is the family, close monitoring of that group could somewhat resolve this problem, which is now discussed in P23L528-532. Nevertheless, other secondary transmissions under quarantine require further unsupported assumptions. At least, we believe that the initial determination of the optimal length of quarantine (i.e. our primary outcome of the present study) should be based on our current approach that strives to avoid excessive complexity.

We greatly appreciate the above comments of the reviewers and their efforts in helping us improve this manuscript. We hope the critique has been appropriately addressed and that the manuscript is now suitable for publication.