Author’s response to reviews

Title: A Double Epidemic Model for the SARS Propagation

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PDF covering letter
Dear the Editors,

In response to your notification of decision concerning our submitted paper

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A Double Epidemic Model for the SARS Propagation
Tuen Wai Ng, Gabriel Turinici and Antoine Danchin
BMC Infectious Diseases

please find below our responses and answers to the reviewers’ comments. Let us add that not only all comments and questions from the reviewers are addressed in this letter but also all of them have occasioned modifications to our manuscript (either because additions to the work were requested or because further clarifications were added where not sufficiently explained, as proven by the reviewers’ questions).

We trust that the manuscript is now in a form which is suitable for publication,

Sincerely,

Tuen Wai Ng
Corresponding author, on the behalf of all co-authors
Fred Brauer’s first comment (ref # 1)

In the model on p. 7, N in the denominator of equations (1) and (5) must represent the total number of live members of the population, because the term I/N is the probability that a contact by a susceptible will be with an infective and thus will produce a new infection. Thus it is necessary to separate disease deaths from the removed class R, and if there are disease deaths it is not possible for the total population size to remain constant.

Authors’ response

The above system of differential equations are derived from the so-called standard incidence approach which is described in [17]. The quantity r/N is actually the average number of adequate contacts (i.e., contacts sufficient for transmission of disease A) of a person per unit time. Then (r/N)I is the average number of contacts with infectives per unit time of one susceptible, and (r/N)IS is the number of new cases of disease A per unit time due to the S susceptibles. Note that here I/N is simply a normalization factor and that has no probabilistic meaning. One can also interpret rP in a similar way. One advantage of this approach is that we can compare the values of r and rP in different cases directly. Moreover, it has also been pointed out that the standard incidence approach is more realistic for human disease than the simple mass action incidence approach (see [17], p.142).

We have included this comment in the corrected version of our manuscript.

Fred Brauer’s second comment(ref # 2)

The parameters a, b, aP are properties of the disease and should be the same in each case. Thus they should be set first before the parameters r and rP are chosen to fit the data. Also, the parameters are given to more decimal places than is warranted by the data.

Authors’ response

We agree that the parameters must follow the physics of the interaction and they should not affect much the outcome of the model. However, there are also some good reasons for the varying this parameters in different cases and therefore a,b, aP may be estimated similar to the parameters r and rP.

The parameters a and aP describe the removal from the classes I and IP to the classes R and Rp respectively. Since the removed classes R are considered to contain the individuals with infections the parameters a and aP characterize the identification rate of potential cases; it is then rather related to the health policy than to the disease itself (e.g. a is not the mortality rate!). Since health policies vary from places to places and the parameters a and aP are not directly related to the disease itself these parameters are not to be considered known but will rather be computed by fitting the simulation results to the data. The parameter b describes the evolution from the exposed class E to the infectives class I; its reciprocal 1/b is related to the latent period of the disease; as such it is indeed more characteristic of the disease itself than the parameter a but it may still be affected by
the geographic region. For instance, the lifestyles of the people in Beijing and Inner Mongolia are very different because Beijing is the capital, and hence much richer (with better hygiene, but with terrible air pollution). The value of the parameter $b$ will also be obtained from the fitting procedure.

Finally, our approach that not fixing the parameters $a$ and $b$ at the very beginning but rather than estimating them form the data can let us to indirectly verify the double epidemic hypothesis. In fact, as already pointed out in the paper, $1/a+1/b$ can be considered as the incubation period plus the onset to admission interval. For the two Hong Kong scenarios we considered, our estimations are quite close to the observed figures (as given by the reference 18).

We have modified our manuscript accordingly to explain why these parameters are to be optimized too and have suppressed irrelevant decimals in the parameters, as rightly suggested by the reviewer.

Fred Brauer’s third comment(ref # 3)

A double epidemic explanation seems to require that an outbreak triggered by a small number of long distance travellers (e.g., Toronto) must come from both epidemics. Is it not possible to get a good fit to the data by assuming a fraction of the population immune at the start, rather than a dynamic process of acquiring immunity?

Authors’ response

We have tested something similar before by setting the total population to something less than the real population but the results were not satisfactory. We can thus safely say that some partial tests have been carried on that indicate that the two spreads are co-existing but that more testing is needed to certify this result. This point is mentioned in the paper.

The reviewer refers to what we called the “static” protection assumption; this hypothesis was tested by setting the total population to several initial values less than the real population (see also the case a) of Hong-Kong simulations) -this is equivalent to what the reviewer suggested- but the fit quality was generally less satisfactory than in the case of the co-existing epidemics (i.e. “dynamic” effect) ; more testing is needed to fully certify this conclusion.

These remarks were added to the text.
**R.Levin’s first comment (ref 3a)**

In the equations there is no latency for virus B. If Virus B is totally unrelated to virus A this may be plausible but if it is a mutant variant of A the assumption should be justified.

**Authors’ response**

We fully agree with the referee that it may be interesting to undertake this study; however, at least for now, the inclusion of the latency for the disease B will imply the introduction of one additional parameter $b_P$ and will further complicate the model. As we stated in our discussion, the more parameters the less convincing should a model be. We are therefore limited today by the lack of clinical studies and statistics on the “protective” epidemic, but as soon as the features of this epidemic are better understood, it will be of major interest to explore this pathway, as suggested by the referee.

Moreover, since the main purpose of the paper is to provide some indirect evidence that a double epidemic may exist, our simpler model may already be good enough for this purpose because of the following reasons. Firstly, even if the diseases A and B are generated from similar viruses, they can still be quite different (for instance at the level of the physical location of the infection) and therefore they need not share similar models. Secondly, since we only want to study phenomena that immunize people from the initial $S$ class, the details of the (SIR or SEIR-like) spread of the protective disease B are less important that those of the propagation of the epidemic A. Within some approximation - discussed below- this two viruses study is only interesting if we want to explain the gastro-enteritis removed class (but we are not aware of any statistics on it). The limit of this conclusion is that if immunization is only obtained upon removal i.e. for the people in the $R_P$ class -and once infected by the protective virus i.e. as soon as they leave the $S$ class as we now suppose- the dynamics of the protective disease become important again.

Comments that present this remarks were added to the paper.

**R.Levin’s second comment (ref 3b)**

In Hong Kong, $r > r_P$ but this relation is reversed in Beijing and Inner Mongolia. This deserves some comment.

**Authors’ response**

The values of $r$ and $r_P$ depend on how the daily contact patterns of people. The usual number of social contacts of a person is in general higher in big city like Beijing while lower in remote area like Inner Mongolia. This may explain the difference of the $r$ and $r_P$ values in these two cases.

This comment was included the text of our manuscript.

**R.Levin’s third comment (ref 3c)**
While the $r$'s are related to contagion rates that may depend on the hygienic situation, the $a$'s and $b$ are closer to clinical properties of the infection. That they differ so much is surprising. In particular, the $b$ value for Inner Mongolia is $76 \times$ that of Beijing, implying that latency lasts so much longer in Beijing. Or is this a misprint? It is not obvious how underreporting affects the parameter estimates.

Authors’ response

The surprisingly high value of $b$ is actually what we have obtained from the fit procedure. One explanation is that there may be a difference in the spread of the "protective" epidemic, that might have started earlier at one of those places. Another explanation is due to the latent immunodepression of the people there: note that they were recently more or less submitted to a severe draught, which meant that they were probably undernourished.

R. Levin’s fourth comment (ref 3d)

The attempts to contain the spread of SARS act by reducing the $r$'s, while more rapid identification of the disease may reduce $b$. Could the authors apply their model to different degrees of effectiveness of quarantine measures in order to determine how good we have to be to stop the spread?

Authors’ response

We also agree that this is important but for now the model has too many parameters to give reliable quantitative results; the qualitative conclusions that can already be drawn were very clearly identified by the referee and are better emphasized in the revised manuscript.