Author's response to reviews

Title: Mitigation of infectious disease at school: targeted class closure vs school closure

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Author's response to reviews: see over
Dear Editors,
please find enclosed a revised version of manuscript MS 6851518521414365 titled “Mitigation of infectious disease at school: targeted class closure vs school closure”

We are grateful to the Reviewers for their positive evaluation of our work. Reviewer J. Kelso writes that “this is a good study that fills in a blind spot in similar earlier simulation studies”. Reviewer Timo Smieszek considers our manuscript to be “a well-written and informative manuscript about a very topical problem” and writes that “the manuscript discussed here is a relevant addition to the scientific literature in this field”.

We are also grateful for the suggested revisions that we have taken into account in the revised version of the manuscript. We believe that this revised version is more accurate and clearer than the original version, and that we have addressed all the issues raised by the Reviewers.

We enclose hereafter a detailed answer to all the remarks made by the Reviewers, detailing the corresponding changes we made to the manuscript and the additional sensitivity analysis we have performed and included in the Additional file. We thank the Reviewers for their comments and we dare to hope that the manuscript is improved and now suitable for publication.

Best regards,

The Authors

V. Gemmetto, A. Barrat, C. Cattuto
Detailed answer to the reviewers’ comments

Answer to Reviewer 1: J. Kelso

We thank the reviewer for his careful reading of the manuscript and his positive comments. We thank him for the suggested revisions that we have taken into account as follows.

Minor Essential Revisions
MER1 Background, para 2, “have led to question” -> “have led some to question”.
MER2 Background, para 2, “benefit of school closure [] and prompt” -> “benefit of school closure [] and has prompted”
MER3 Background, para 3, ”two accounts: First” -> “two accounts. First”
MER4 Background, para 3, “allow to develop” -> “allow the development of”
MER5 Methods, Epidemic model, para 1 “consider a stochastic” -> “consider an individual-based stochastic” (The Background does mention the fact that the model is an individual-based one but this should also be stated in the Methods, since this fact is essential for anyone trying to reproduce the method.)

We have performed all these corrections.

MER6 Methods, Epidemic model, para 1 What was assumed about the force of infection when a susceptible person was in contact with 2 or more people at the same time ? Was the same beta value used, or did forces of infection add ? Also, a little more information on what sort of stochastic simulation was used would be helpful eg was the Gillespie algorithm used, or Tau-leaping (in which case, what time step was used ?).

Possible transmission events are evaluated independently so that forces of infection add. We have added a footnote on this point. We have also precised that we use a simple temporal iteration with time-step given by the data resolution, i.e. 20seconds.

Corrected.

MER7 Methods, Epidemic model, para 2 ”during a time interval dt” -> “during a small time interval dt”

Corrected.

MER8 Methods, Epidemic model, paras 4 and 5: In addition to giving the beta rate parameters as frequencies, can you also give them (maybe in parenthesis) as mean periods between events. “24 minutes” is more helpful to the reader than “6.9x10e-4 Hz”.

We have added these values.

MER9 Methods, Simulation and analysis ”of lost school days defined by” -> ”of lost school days, defined by”

Corrected.

MER10 Conclusions, para 4. The last part of the paragraph, from ”Another limitation of this study is the simplistic coupling ...” is very important. It should have its own paragraph, and could be expanded some more.
In particular, what the authors have established is the effectiveness of school closure in reducing the epidemic size "in the school population" - infection in the rest of the community is not modelled.

The reduction in the epidemic in the school population is very important however, because it is fairly well established (as is pointed out in the introduction) that effective school closure interventions also reduce infection throughout the whole community indirectly, even for people with no contact with children.

We have put this part in a separate paragraph and added a sentence about the possible feedback effect to the spread in the whole community.

MER11 Reference 20 has capitalised author names
This has been corrected.

MER12 Reference 33 should have a access date ?
We have added an access date.

**Discretionary Revisions**

DR1 Given that this is being considered for BMC Infectious Diseases and not a modelling journal, the title should indicate that it is a modelling study eg perhaps "Mitigation of infectious disease at school: modelling targeted class closure vs school closure".

We prefer to keep the title as it is but we have made more precise in the abstract that we design models and that we model the mitigation measures.

DR2 Abstract, sentence 2 is long an confusingly punctuated. It might be better to split it up into two sentences.

We have rewritten and split this sentence.

DR3 Abstract, sentence 3, "contact networks in" -> "contact network data from"

Corrected.

DR4 Results, para 1: see MER7

We have added the value of $1/\beta$ in minutes.

DR5 Results, Effect of risk of infection in the community, last para. The effect that is apparent in Table 2, whole school closure is less effective than targeted class and grade closure is interesting. I think what is going on here is an example of the phenomenon where for effective interventions of limited duration it is possible that to begin the intervention "too early". (You can show this with a very simple toy deterministic SIR model, eg try a model that starts out with $R_0=1.2$ that switches to 2.0 after 10 gamma time periods, representing the relaxation of an intervention; and then do the same but start with $R_0=1.5$, representing a less effective intervention. The second one has a lower final attack rate, and the first one does better if you delay the start of the intervention but keep the same duration.)

The evidence that this is what is happening is, as the authors point out, in Figure 3 with the curve with two epidemic peaks. The whole school closure is very effective when it is introduced, but when it is relaxed the epidemic resumes, and the result is
more infections than a less effective intervention applied for the same period. Notice that with closure threshold 3 for 120 and 144 hours, the whole school intervention is better - this is because the intervention continues long enough that the “rebound” does not occur. For a trigger threshold of 2, the intervention starts even earlier (presumably), and even with 120 hours of closure the whole school closure is worse than targeted closure. I predict that if you tried a trigger threshold of 4, whole school closure would outperform targeted closure with eg 96 hours of closure. I suggest you mention that the poor performance of limited duration all-school closure could be because the intervention is being applied too early. Unfortunately, I can't help you with a reference for that. I presume this effect is fairly well known, although I've never found a publication describing it. I noticed the effect in some influenza simulations, and talking to some other modellers found that it is "known folklore".

We agree with these points and have added a comment.

DR6 Conclusions, para 1 "children from the" -> "children of the"

Corrected.

DR7 Conclusions, para 1 "mitigate the epidemic and in terms of their impact on the schooling system" More targeted strategies should mitigate the impact not only on the schooling system, but also on the whole community, give the social and economic cost of school closures.

We agree with this point and have added comments on this in para 1 and 2 of the conclusions.

DR8 Conclusions, para 4 Regarding the robustness of results to the re-use of the limited amount (2 days) of contact data. If you did 2 lots of additional simulations where you used a single day's data for all 4 school days, and found similar results, that might provide a little bit of evidence that adding more days of real data (were they available) would not change things.

We thank the reviewer for this suggestion. We have indeed performed such simulations and found very similar results. In order not to overload the Additional files with additional data, we do not show the corresponding results but we have added a comment in a footnote in the conclusions.

DR9 Conclusions, para 5 A natural follow-up to this study would be to use the same school population model, but to add a larger community to the model eg family members, additional households without school-aged children, workplaces. Contact in these additional settings would not be supported by the same high-fidelity contact data and would only be an estimate, however such a study would be valuable because (a) it would eliminate the possibility that not coupling the school transmission dynamics to the community transmission is distorting the outcome, (b) it would verify (and quantify) that school closure has a knock-on effect in the rest of the community.

We agree with this point. Our conclusions already mentioned as a future avenue of research a refinement of the coupling with the community. We have expanded this part by inserting a comment on the possibility to quantify a possible feedback effect in the community.
DR10 Conclusions, para 5. Regarding strategies involving closing single schools or multiple schools in a geographic area - a study by Halder et al (including myself) in BMC I.D. in 2010 ("Developing guidelines for school closure interventions to be used during a future influenza pandemic") looked at this question, along with duration of closure and trigger thresholds, although of course not with a detailed school contact model.

We thank the reviewer for this reference that we were not aware of and that we have added.

DR11 Conclusions Your presentation of sensitivity analysis results in the additional file is good. You might note in the main manuscript that the results from the benchmarking strategies (iv) and (v) establish that the effect of the class-targeting strategies really is due to the targeting of contacts of cases, and not just the size of the closure (ie single class).

We thank the reviewer for this comment and now mention these results in the conclusions.
Answer to Reviewer 2: Timo Smieszek

We thank the reviewer for his very positive appreciation of our work. We are also grateful for the comments and suggestions. that we have taken into account as follows.

1) Abstract: the authors use the term "airborne infections", a term which I think is misleading in the context of your manuscript. One should distinguish between truly airborne infections and droplet-transmitted infections. While the former term refers to infectious diseases that spread via aerosolised particles that stay suspended in the indoor air for extended periods of time (and, hence, don't require the kind of social action the authors modelled here). The latter refers to infections that spread primarily via droplets of larger size that fall out rather quickly and for which social interaction - as measured and modelled here - might be a good proxy (Cf. e.g., Indoor Air 2007, 17:211–225; see also discussion in BMC Infectious Diseases 2014, 14:136). In short: your model only applies to infections transmitted primarily by larger droplets, not to truly airborne infections. It would be interesting to discuss also what the differences for airborne / aerosol transmitted infections might be.

We agree with the reviewer. We have removed the term ‘airborne’ in the abstract and replaced it by ‘droplet-transmitted’ in the introduction. The distinction between airborne and droplet-transmitted goes beyond the scope of the present paper so we did not add a discussion on this point.

2) P. 1: "It has been long known [1,2] that children play an important role in the community spread of infectious disease, in particular influenza"; a relevant addition (since it triggered the respective vaccination programme in the UK) might be the following paper: PLoS Med 10: e1001527.

We have added this reference.

3) P. 2: "...and more recently wearable sensors that detect close-range proximity [30,31,32] and face-to-face contacts [33,34,36,37]"; I don not see a fundamental difference between the TelosB motes and the SocioPattern sensors in terms of what they measure. Salathe's contacts are also face-to-face (see, e.g., supplementary figure S4 in Salathe's PNAS paper).

We have shifted the reference to Salathe's paper to reflect that it deals also with face to face contacts.

4) P. 2: "This is expected to be a rather general feature of schools, due both to age homophily [38] and schedule constraints"; I agree that there are these tendencies in all schools (especially age assortativity), but I think that the extent depends vastly on how a school system is organised. There is probably a difference between primary and high school, and there is certainly a difference between, e.g., US and central European schools. The way the US high school system works makes the contacts there more random / less structured (cf. the Salathe group papers) than contacts in a typical European school. I would tone that statement down a bit and discuss potential differences. Maybe a comparison between your data and the Salathe data (with respect to the research question of the manuscript presented here) would be an interesting task for the future?

We thank the reviewer for this comment. We agree with this point: we have toned down this comment by mentioning that this effect is qualitative, adding a footnote.
about a possible dependence on type of school and countries, and added a comment in the conclusions (limitations). As also mentioned in the conclusions, it is important that no detailed knowledge of the contact patterns within the school is actually needed to define the strategies, but only limited information, in the same spirit as Ref 53 by Smieszek and Salathé.

5) P. 3: "In such a compartmental model each individual at a given time..." from my point of view, your model is not a compartmental model. Since you incorporated the measured contact structure into your model, it must be individual-based. Compartmental models are ODE models that don't represent individuals explicitly, but bin them into "boxes" aka compartments.

We have removed the word ‘compartmental’.

6) P. 4: The authors' model assumptions:
6.a) Did you do sensitivity analyses on your most crucial / shaky-ground assumptions, e.g., that asymptomatic individuals are beta/2 or that the probability of being asymptomatic is 1/3?

These values of the parameters are commonly assumed in many models of influenza spread (both compartmental or agent-based), without any sensitivity analysis. In particular, the probability of being asymptomatic is also consistent with estimates from empirical studies. We have added references to various works. We also add in the Additional File 2 the results of new simulations in which the probability of being asymptomatic is ½ (as the literature typically indicates that this value is between 30% and 50%). The probability of a large outbreak is higher than with p_A=1/3, but the results are qualitatively similar.

6.b) Why do you model recovery as a fixed rate (exponential distribution of infection duration)? More realistic would be log-normal / Weibull distributions for the infection duration. Since your model appears to be individual-based (cf. my comment 5), I cannot see a striking mathematical reason to use the (less realistic) exponential distribution. Could you, at least, comment on the implications of this assumptions on model results?

We have here to apologize for an imprecision in the manuscript. We were in fact using Gaussian distributed times of latency and infection, of averages 1/\mu and 1/\gamma and with rather small values of the standard deviation, giving results similar to cases with fixed latency and infectious period durations. We have made this more precise in the text, and have performed additional simulations using Weibull distributions of latency and infection times, with two different values of the shape parameter of the Weibull distribution. Our main results are robust with respect to such changes: the precise numbers depend slightly on the choice of the distributions, as expected, but the comparison between the different strategies, which is the main point of our study, remains valid. We report in the Additional file 2 the corresponding results.

6.c) Where do your beta-values come from?

We have adjusted the beta values in order to obtain values of R0 close to 1.5, as in Stehle et al. (2011) and Machens et al. (2013). We have added a footnote on this point.

6.d) A source of references for some of your parameters might be BMC Infectious Diseases 2011, 11:115.
We have added a series of references, including this one, about the choice of parameters.

7) P. 7: "inside one school, children do not mix homogeneously" - pls. see my comment 4

We have modified this sentence to make it more specific.

8) Tables 1-5: It would be great if you could compare not only "targeted class", "targeted grade", and "whole school", but also a baseline of doing nothing / implementing no intervention.

Tables 1, 2, 4 and 5 already contain the results obtained in case of no intervention (first line of each table "No closure"). For Table 3, the number of lost days in the case of no intervention is 0. We have added in each caption the precision that the case of no intervention is given, and in Table 3 the case of no intervention.