Author’s response to reviews

Title: Non-Pharmaceutical Public Health Interventions for Pandemic Influenza: An Evaluation of the Evidence Base

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Author’s response to reviews: see over
Dear Ms. Brown:

Attached please find our revised manuscript, “Non-Pharmaceutical Public Health Interventions for Pandemic Influenza: An Evaluation of the Evidence Base,” to be considered for publication as an article in *BMC Public Health*. We appreciate the opportunity to revise our manuscript and found the comments of the peer-reviewers extremely helpful in improving the clarity of our analysis. We have addressed the specific comments made by the reviewers and have fully incorporated the requested revisions into the manuscript. As requested, we have included in this cover letter a point-by-point list of responses, revisions and/or rebuttals to each of the reviewer’s comments.

Thank you very much for your consideration of our revised manuscript. We look forward to hearing from you.

Sincerely,

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Response to Reviewer 1 comments:

This is an important topic, which needs to deserve attention, since there are no many papers analyzing the level of evidence of most of the items in preparedness plans against the next pandemics. However there are several drawbacks in this paper limiting its interest.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Although this is the goal of the paper, there is no clear reference to the level of evidence used in any part of the paper. What are the respective weights allocated in recommendations based from studies and data or from expert opinions (panel experts)? There is no definition of what is a "controlled study“? Do the author mix randomized control trials and case-control studies in a same level of evidence?

We took several steps in response to the reviewer’s comment. First, we revisited our initial search and updated it to include relevant articles from 2006 and 2007 (previously the search had ended in December 2005). Second, using a modified rating scale from West et al (2002), we formally rated the strength of the scientific evidence from each of the relevant articles we reviewed. We present our results in Tables 1 and in a new Table 2 (page 21), which describes the modified rating scheme and the number of individual articles that fell into each category. The formal rating process served to confirm our initial report of a lack of evidence on the efficacy or effectiveness of most non-pharmaceutical interventions for influenza. Given the dearth of scientific evidence on the use of non-pharmaceutical interventions for influenza in a pandemic setting, we did not attempt to allocate weights to the overall weak evidence. Rather, we used expert opinion precisely because of the lack of confirmatory studies in our topic of interest.

We added new text (in boldface) describing this analytic process:

On page 5: “The search identified 2,552 titles, of which 168 were eventually selected based on general relevance. Exclusion criteria are presented in Table 1, and a list of the final articles selected for full review is provided in Appendix B. Using a modified rating scale from West et al., we then formally rated the strength of the scientific evidence in each of the relevant articles. Table 2 describes the modified rating scheme and reports the number of individual articles that fell into each rating category.”

On page 7: “Our formal ratings of the articles revealed few high quality studies to inform the evidence base for non-pharmaceutical interventions for influenza. The majority of topically relevant articles we identified were narrative reviews, case reports, observational studies or expert opinion, editorials and commentaries (Table 2). We found only 9 systematic reviews of relevant material and 3 randomized clinical trials. Additionally, few of the topically relevant articles were directly on-point.
In light of the evident lack of scientific evidence about specific non-pharmaceutical interventions in the context of seasonal or pandemic influenza, there was limited directly usable information from the majority of the studies identified in the formal Medline search. For this reason, we turned to expert opinion to inform and categorize the findings. Expert panels are often used to develop guidelines and recommendations when compelling evidence is lacking. Drawing on both qualitative discussion at the expert panel and quantitative results from the follow-up survey discussed above, we classified the non-pharmaceutical interventions into two broad categories, those whose use was recommended by the panel and those whose use was not recommended. Figure 1 summarizes the results from the survey questionnaire, providing the complete list of non-pharmaceutical intervention-setting-phase combinations that were queried and the number and proportion of items for which there was agreement (41.5%) or disagreement (58.5%). We included relevant findings from the literature, where available, in our discussion of the specific interventions, and we cited some of the selected studies from the formal Medline search, as well as others that supplemented the search, to provide necessary background information when appropriate and to support some commonly held views about infection control activities. We also note below interventions about which there was disagreement or no recommendation by the panel.”

Regarding hand washing: there are no practical recommendations. How often should that be recommended? What is the expected level of risk reduction, in terms of relative risk, since "controlled studies" are advocated to support the recommendation, such estimates should have been published.

Our aim was to assess the evidence base as a starting point for further research and for the eventual development of evidence-based guidelines in the context of a pandemic. As such, we did not provide practical recommendations for any one non-pharmaceutical intervention. Irrespective of our intention, we did not find specific estimates of the expected level of risk reduction from hand-washing for influenza, either in the literature or among the experts. Finally, the hand-washing studies that we did review generally did not specify “doses”, and those that did were limited to bacterial agents.

Regarding surveillance and rapid viral diagnosis, it is said that there is no evidence on the efficacy of surveillance and case reporting, but rapide viral diagnosis is considered as "necessary to increase its adoption in the US health services" without reference to any evidence regarding its efficacy.

This recommendation is based on expert opinion. We have modified the statement to clarify the source.

On page 10: “Moreover, since viral diagnosis of influenza is currently not routine practice, the experts reasoned that education regarding the importance of improved tests will be necessary to increase the adoption of such tests in the U.S. health system.”
Regarding masks, there is no reference to the SARS experience which was published with strong evidence of a protective effect (including some assessment of hand washing too). It is not mentioned that other advantage of using masks is that they will induce no resistance, and cause no shortage in supply.

Although there is a wealth of information about infection control strategies, including the use of N-95 respirators and surgical masks that emerged from the management and containment of SARS the experts on our panel l urged caution in applying lesions from SARS to an influenza outbreak. We have added text to address the issue of resistance.

On page 10-11: “Moreover, surgical masks and N95 respirators were recognized as a non-invasive technology that would induce no antiviral drug resistance.”

**Minor Essential Revisions** (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Figure 1 is only quoted once in the results section regarding hand washing. Should be better explained and quoted.

We have introduced and described Figure 1 in the results section.

On page 7: “Drawing on both qualitative discussion at the expert panel and quantitative results from the follow-up survey discussed above, we classified the non-pharmaceutical interventions into two broad categories, those whose use was recommended by the panel and those whose use was not recommended. Figure 1 summarizes the results from the survey questionnaire, providing the complete list of non-pharmaceutical intervention-setting-phase combinations that were queried and the number and proportion of items for which there was agreement (41.5%) or disagreement (58.5%). “

**Response to Reviewer 2 comments:**

**Reviewer's report:**
This paper is a useful contribution to understanding the role that non-pharmaceutical interventions may have in a future influenza pandemic. I think the degree of skepticism is appropriate. My major concern is that the literature is not used in a transparent manner (see below).

**Major Compulsory Revisions** (that the author must respond to before a decision on publication can be reached)

The authors do not appear to have actually used all of the 156 title selected for the study (there are only 55 references cited), hence I have no way of knowing whether the authors have selectively used the literature, as opposed to presenting and impartial summary. What was contained in the 100 studies that weren't cited? If they were uninformative then
say so. If not, I would like to see a table that summarizes the results of the studies in an informative way.

We appreciate the reviewer pointing out the confusion caused by the omission of the selected references. We clarified our analysis in several steps described above under the major compulsory revision of Reviewer 1. As discussed above, we also generated Table 2 (page 21) in response to this reviewer’s comment, to make explicit both our rating scheme and the final strength of the evidence base. In addition, because *BMC Public Health* submission requirements permits only up to 40 references (and we included 56), we have included in an Appendix a list of the articles that we found most relevant to our study, and that we rated. In light of the lack of evidence, we largely relied on expert opinion precisely because of the lack of confirmatory studies in our area of interest. We did, however, draw from some of the studies we identified, as well as others that supplemented our formal Medline search, to provide necessary background information in the manuscript and to describe some commonly held views about infection control activities.