PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protection levels of N95-level respirator substitutes proposed during the COVID-19 pandemic: safety concerns and quantitative evaluation procedures
AUTHORS	Ballard, David; Dang, Audrey; Kumfer, Benjamin; Weisensee, Patricia; Meacham, J; Scott, Alex; Ruppert-Stroescu, Mary; Burke, Broc; Morris, Jason; Gan, Connie; Hu, Jesse; King, Bradley; Jammalamadaka, Udayabhanu; Sayood, Sena; Liang, Stephen; Choudhary, Shruti; Dhanraj, David; Maranhao, Bruno; Millar, Christine; Bertroche, J; Shomer, Nirah; Woodard, Pamela; Biswas, Pratim; Axelbaum, Richard; Genin, Guy; Williams, Brent; Meacham, Kathleen

VERSION 1 – REVIEW

REVIEWER	Dong, Yanhong National University of Singapore, Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine
REVIEW RETURNED	01-Nov-2020

GENERAL COMMENTS	This paper aims to evaluate the efficacy and fit of improvised N95 respirator solution using University lab based protocols. This is important to ensure the safety of available N95 respirator to be used for pandemic. The authors described in details the protocols for materials testing. However, the study did not recruit participants for sizes other than small and regular size commercial N95 respirators. Consequently, the results are less generalizable. Additionally, the number of participants were not reported. This limits the study to be replicated. Therefore, the acceptance of this paper cannot be recommended.

REVIEWER	Boskoski, Ivo Digestive Endoscopy Unit. Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia., Digestive Endoscopy Unit
REVIEW RETURNED	02-Nov-2020

GENERAL COMMENTS	Ballard et al investigated the protection levels of N95 respirators for the Covid pandemic. The article is very well written and the results are impressive. This multidisciplinary working group did great job. Shortages of filtering facepiece respirators is an essential issue. It is important to discuss (shortly) the techniques for re-use/sterilization of respirators (see and cite PMID: 32353457, PMID: 19805391).

REVIEWER	Guerra, Patrick University of Cincinnati
REVIEW RETURNED	09-Feb-2021

GENERAL COMMENTS	This study provides timely and important information that can be extremely helpful, e.g., for frontline healthcare personnel, during the current COVID-19 pandemic and future public health crises. The authors should provide more information (see below) to make their paper clearer to readers. Comments: (1) Instead of “solutions” in the title and throughout the text, the authors should instead use “alternatives” or “substitutes” (as used in the manuscript), since the outcome of their work is that the “solutions” they examined failed and were insufficient. The authors could also clarify by saying “potential solutions”. (2) Page 7: The authors state that during crises, respirators may need to function over extended use and be reused. Therefore they should be suitable to sterilization. Do the authors mean that this is a current feature of respirators or that this is a desired or recommended feature that may not be present? (3) More information is necessary in the methods and results of this study to make it clearer to readers, and in order to better examine the outcomes of the different tests. For example, why did the authors pick the five respirator designs that they tested in this study? What were the criteria for choosing and including these open-source designs? How did the authors search for designs? Was the process for finding and choosing designs for testing systematically done, e.g., systematic online search, or was it done via other means, e.g., word-of-mouth or those immediately known by the authors? Were there any designs that were found that were precluded from use in this study? If so, why? Are these the only open-source designs out there? The authors need to include this information to address any potential search and sampling bias by the authors, which might affect the data that are collected and the narrative of the paper. How many replicates (both sample and technical) were performed for each of the five respirator designs? How did the authors find and select materials for particle filtration performance? What were the sources of these materials? The authors state that particle filtration efficiency values that were reported in their study were the average of three to four different filter punches for the same material. Were these filter punches (Supplemental Table 1 and Figure 4b) from the same source material sample (n=1) or from three to four distinct samples of that source material type (n=3-4)? If the different punches were all from the same exact sample, then the authors have several technical replicates for a single sample piece, but only one sample per type for comparing between the different materials. This should be made explicit. If the authors only have n=1 for each material type, the authors could qualify their data as more preliminary but still cautionary for end users of improvised N95 alternatives.

	How were the data in this study, e.g., in Supplemental Table 1 and Figure 4b, tested statistically? This could be clearer.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Yanhong Dong, National University of Singapore
Comments to the Author:
This paper aims to evaluate the efficacy and fit of improvised N95 respirator solution using University lab based protocols. This is important to ensure the safety of available N95 respirator to be used for pandemic.

The authors described in details the protocols for materials testing.

Thank you, Dr. Dong, for your detailed reading of the paper and the critique that follows. We have edited the manuscript carefully to address the critical issues that you raise.

However, the study did not recruit participants for sizes other than small and regular size commercial N95 respirators. Consequently, the results are less generalizable. Additionally, the number of participants were not reported. This limits the study to be replicated. Therefore, the acceptance of this paper cannot be recommended.

Thank you for identifying this ambiguity in the original submission. The revised manuscript now lists the number of participants in the abstract, as follows:

“Participants: Seven adult volunteers with who passed quantitative fit testing for small (n=2) and regular (n=5) size commercial N95 respirators.”

Additionally, we thank you, Dr. Dong, for pointing out to us that we were unclear about the nature of the contribution, and for making clear to us that the writing misrepresented the work. The manuscript has been revised to make clear that the focus of the manuscript is presenting protocols that can be replicated by others, and not the development of statistically significant datasets on these mask prototypes. We have therefore added the following text:

(P17/pdf-P20 line 35-53): “To demonstrate these protocols, fit testing was carried out with a limited number of individuals who passed fit testing of analogous small and regular size N95 respirators. For designs such as the elastomeric design, which was the only one to passed the fit test for any of the 7 volunteers, additional testing would be warranted for each individual who used this design. Although this limited testing was not designed to develop statistically significant datasets on the proportion of the population that might be able to use each mask design effectively, it did serve to both demonstrate repeatable protocols and to establish limitations of the designs that were not sufficiently pliable to pass fit testing for any of the volunteers.”

To further bring out the reviewer’s point in the revised manuscript, we now emphasize this point in the discussion as well with the following text (P14/pdf-P17 L31-55): “The focus of this paper is protocols that can be applied to test the function of improvised masks. When demonstrated on a limited number of volunteers, results revealed that most designs were not sufficiently pliable to match the contours of any of the volunteers, and therefore suggested that these designs might benefit from revision of form or materials that would improve fit prior to mass production. For the one mask that did

fit a portion of the volunteers, results emphasize that careful fit testing would be required for each user of the technology. We note that the failure to fit some volunteers is not a failure of the design, in that an improvised design that performed well for individuals with only small and regular faces would still have large benefit in alleviating crisis shortages such as those encountered during the COVID-19 pandemic. In one cohort medium and large sizes were grouped together and only represent 50/229 (21%) of the cohort. In addition, with the same protocols required for individuals using a commercial N95 respirator in an occupational setting, fit testing could be used to verify that a particular design had adequate fit for a given individual's face."

Reviewer: 2
Dr. Ivo Boskoski, Digestive Endoscopy Unit. Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia.
Comments to the Author:
Ballard et al investigated the protection levels of N95 respirators for the Covid pandemic. The article is very well written and the results are impressive. This multidisciplinary working group did great job. Shortages of filtering facepiece respirators is an essential issue. It is important to discuss (shortly) the techniques for re-use/sterilization of respirators (see and cite PMID: 32353457, PMID: 19805391).

Thank you, Dr. Boskoski, for your supportive comments, for suggesting this line of discussion, and for bringing these important references to our attention. We note that Dr. Guerra (reviewer 3) also raised this suggestion. The following has been added to the introduction (P4/pdf-P7 line 17-24): "More specifically, supply of commercial N95 respirators has been conserved during the COVID-19 pandemic by multiple sterilization methods including hydrogen peroxide vapor, chlorine dioxide vapor, steam, ultra-violet radiation, heat, and isolation over time."

Reviewer: 3
Dr. Patrick Guerra, University of Cincinnati
Comments to the Author:
This study provides timely and important information that can be extremely helpful, e.g., for frontline healthcare personnel, during the current COVID-19 pandemic and future public health crises. The authors should provide more information (see below) to make their paper clearer to readers.

Thank you, Dr. Guerra, for your consideration and your thoughtful comments.

Comments:

(1) Instead of "solutions" in the title and throughout the text, the authors should instead use "alternatives" or "substitutes" (as used in the manuscript), since the outcome of their work is that the "solutions" they examined failed and were insufficient. The authors could also clarify by saying "potential solutions".

Thank you for noting this indeed an important distinction and for noting the shortcomings of our original title. The title was changed to "Protection levels of potential N95-level respirator substitutes proposed during the COVID-19 pandemic: safety concerns and quantitative evaluation procedures," and instances of "solutions" were revised to "potential N-95 respirator substitutes", "potential substitutes", or "substitutes". "Solution" was avoided when discussing the open source potential substitutes. Now largely referred to as "designs"

(2) Page 7: The authors state that during crises, respirators may need to function over extended use and be reused. Therefore they should be suitable to sterilization. Do the authors mean that this is a current feature of respirators or that this is a desired or recommended feature that may not be

present?

Thank you for raising this important point, also raised by Dr. Boskoski (reviewer #2, above). In response to both of your suggestions, we added the following to the introduction (P4/pdf-P7 line 17-24): "More specifically, supply of commercial N95 respirators has been conserved during the COVID-19 pandemic by multiple sterilization methods including hydrogen peroxide vapor, chlorine dioxide vapor, steam, ultra-violet radiation, heat, and isolation over time."

(3) More information is necessary in the methods and results of this study to make it clearer to readers, and in order to better examine the outcomes of the different tests. For example, why did the authors pick the five respirator designs that they tested in this study? What were the criteria for choosing and including these open-source designs? How did the authors search for designs? Was the process for finding and choosing designs for testing systematically done, e.g., systematic online search, or was it done via other means, e.g., word-of-mouth or those immediately known by the authors? Were there any designs that were found that were precluded from use in this study? If so, why? Are these the only open-source designs out there? The authors need to include this information to address any potential search and sampling bias by the authors, which might affect the data that are collected and the narrative of the paper.

Thank you for this critique, which emphasizes to us that we were unclear about the nature of our contribution, and that the writing misrepresented the work. The manuscript has been revised to make clear that the focus of the manuscript is presenting protocols that can be replicated by others, and not the development of statistically significant datasets on all potential N-95 respirator substitutes. We have therefore added the following text to the discussion (P17/pdf-P20 lines 11-32):

"Our working group identified designs based upon designs in the published literature, designs in the mainstream media, and designs that were proposed to the Washington University hospital system. Although these designs were by no means exhaustive and their selection represented a degree of media bias, they nevertheless represented a sufficiently diverse sampling of improvisation and innovation to illustrate the need to evaluate efficacy and to demonstrate the protocols that are the focus of this paper. Although this study does not evaluate improvised respirator designs as a category (in which case sampling bias would be of concern), and we did not attempt to test all of the large number of potential N-95 respirator substitutes."

Additionally, we have clarified the methods by modifying the methods section (P5/pdf-P8 lines 14-17): "Five open-source, improvised respirator designs were selected for testing based on their wide public dissemination (during the early COVID-19 pandemic, March-April 2020) in order to demonstrate testing procedures and identify efficacy and potential limitations…"

How many replicates (both sample and technical) were performed for each of the five respirator designs?

Thank you for noting this oversight in our manuscript. For the quantitative fit testing, each design was tested by 2 individuals with small faces and 5 individuals with regular faces. For the filtration and breathability materials testing, 3-4 separate punches were tested. For the splatter and liquid repellency materials testing, 1-3 separate material punches (based on availability) were tested. To address this oversight, we have added the following text:

(P17/pdf-P20 lines 34-53): "To demonstrate these protocols, fit testing was carried out with a limited number of individuals who passed fit testing of analogous small and regular size N95 respirators. For designs such as the elastomeric design, which was the only one to passed the fit test for any of the 7 volunteers, additional testing would be warranted for each individual who used this design. Although

this limited testing was not designed to develop statistically significant datasets on the proportion of the population that might be able to use each mask design effectively, it did serve to both demonstrate repeatable protocols and to establish limitations of the designs that were not sufficiently pliable to pass fit testing for any of the volunteers."

How did the authors find and select materials for particle filtration performance? What were the sources of these materials? The authors state that particle filtration efficiency values that were reported in their study were the average of three to four different filter punches for the same material. Were these filter punches (Supplemental Table 1 and Figure 4b) from the same source material sample (n=1) or from three to four distinct samples of that source material type (n=3-4)? If the different punches were all from the same exact sample, then the authors have several technical replicates for a single sample piece, but only one sample per type for comparing between the different materials. This should be made explicit. If the authors only have n=1 for each material type, the authors could qualify their data as more preliminary but still cautionary for end users of improvised N95 alternatives.

The materials evaluated for particle filtration performance included those that had been proposed by open-source designers for improvised respirator designs (ex. H500 and H600 sterilization wrap, HVAC filtration material such as MERV16 filters) as well as those available by convenience to our working group (ex. Filti). Where missing, manufacturers have been added to the methods section, with the exception of the HVAC MERV16 material, whose manufacturer is unknown. The following has been added to the methods section to describe the rationale for the selection of these materials (P5/pdf-P8 lines 38-40): "Several of these designs could be fabricated using different filtration media, and we evaluated several candidates that have been proposed for use in these open source designs."

The replicates (n=3 or n=4) represent different filter punches of the same material as described in the methods section (P7/pdf-P10 lines 46-48): "Particle filtration efficiency values reported here are the average of the three to four different filter punches for the same material." As described in the "Supplementary Filtration Methods" section of the Supplementary Material, the filtered and unfiltered particle concentrations are measured over successive periods of thirty seconds with a condensation particle counter. The "Methods of Calculation" section in the Supplementary Material describes how the filtration efficiency and its uncertainty is calculated from these measurements.

How were the data in this study, e.g., in Supplemental Table 1 and Figure 4b, tested statistically? This could be clearer.

The following has been added following Supplemental Table 1: "Replicate intervals represent standard uncertainty, and mean intervals represent 95% confidence intervals."

For Figure 4b, we have clarified the following in the caption: "Error bars for filtration efficiency and pressure drop are 95% confidence intervals for mean values (represented as horizontal lines)."

VERSION 2 – REVIEW

REVIEWER	Guerra, Patrick University of Cincinnati
REVIEW RETURNED	13-Jul-2021

GENERAL COMMENTS	The revised version of the manuscript is significantly improved. My comments are aimed at making the manuscript potentially clearer to readers from the outset (comment 1), as well as a suggestion

	that can make the results of the study more interesting to readers (comment 2). (1) Final paragraph of the Introduction, section starting with "Testing recently developed…" As this is the goal of the present work, i.e., presenting testing protocols for improvised designs and materials for FFR substitutes that can be replicated by others, more emphasis could be made here to better introduce this topic. For example, although the authors point out that many institutions have used improvised FFR substitutes that have not undergone appropriate safety testing, it is reasonable for readers to ask why not. Is it because of a lack of specialized expertise and/or a lack of specific equipment that is required for testing at most institutions? Are such testing methods cumbersome or not critical when using improvised FFR, given the acute shortage in task-specific PPE and the crisis conditions that necessitate the use of improvised FFR in the first place? The authors could provide more background and context for their framework, e.g., their protocols are "user-friendly", can use equipment typically already found at most institutions, or can seamlessly integrate institutional know-how for testing. As this section is only two sentences in length at the moment, the manuscript still gives the impression that its focus is to evaluate the designs and materials used for improvised FFR, rather than the presentation or description of testing methods that need to be done in order to ensure healthcare worker safety. (2) It would be interesting for readers to know if there is a specific order in regards to which testing protocols (i.e., quantitative fit testing, filtration and breathability, liquid repellency and splatter) are done or if the order does not matter. For example, do the authors feel that one type of test is more important out of the sets of tests, e.g., quantitative fit testing? If so, does that mean performing the other tests for a specific improvised FFR design a moot point if it fails this first test? Such a benchmark test, or a hierarchy for tests, might prove helpful to investigators so that they can save time, instead of testing designs and materials that already might be suboptimal with respect to a key test (although I acknowledge that there might be trade-offs when it comes to the attributes of designs and materials). It might also be helpful to readers to provide a workflow diagram outlining the various protocols graphically, e.g., like an algorithm, especially if the authors consider that one type of test is more important than others.