Title: Age-dependent differences in lung ventilation impact influenza-induced tachypnea in the cotton rat

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Reviewer: Kevan Hartshorn

Reviewer's report:

The article by Trias et al provides a useful new model to evaluate differences in the consequences of influenza infection in infants and adults. This is valuable since the morbidity and mortality of influenza is increased in infants. The authors first study respiratory mechanics as they vary with age in uninfected cotton rats. The main findings of interest are that the elastance drops with age. Although TV increases with age it does not keep pace with increased weight so that the ratio of TV to weight drops with age. They authors then evaluate respiratory mechanics after influenza infection in infants and adults. In particular the authors identify tachypnea as a reproducible indicator of infection in both infants and adults. In dissecting out the mechanisms for tachypnea the authors reveal that there are important differences in respiratory mechanics between infants and adults responding to infection. In adults tidal volume is decreased at the time of peak tachypnea (day 2) and minute volume is not increased. In infants tidal volume is not reduced and minute volume is therefore increased. In line with this the peak inspiratory and expiratory flow rates are increased in infants but not in adults. Some of the other parameters studied including relaxation time, time of expiration and Penh are not different between infants and adults (although the peak in Penh seems higher in infants at day 2 no statistical comparison between infants and adults was made here).

The authors also show that the timing of tachypnea seems to correlate best with epithelial cell damage and not peribronchiolitis or interstitial pneumonitis, although no formal statistical correlation studies are attempted.

The discussion is generally good and points out that the increase in minute volume in infected infants could result in greater respiratory fatigue in infants compared with adults.

The data presented is considerable and the experiments seem to be well done. The evaluation of respiratory mechanics during infection is something that is not done in general during mouse models of influenza or other animal models and provides an valuable new way of evaluating the consequences of infection.

The major critiques are as follows:

1. The abstract does not make clear the potential clinical importance of the finding that underlying respiratory mechanics resulting in tachypnea differ between infants and adults. Since the main potential value of the model system
is in elucidating why infants have worse outcome with influenza it would be good to work some of the conclusions provided in the discussion into the abstract.

2. It would be useful to highlight which changes indicate increases in the work of breathing since the discussion emphasizes that respiratory muscle fatigue might be greater for infants leading to respiratory failure. Is there an objective parameter to point to that supports this conclusion?

3. It would be useful to compare statistically the changes occurring in infants vs adults for some parameters (e.g., amount of increase in PEF or PIF or TV or the difference in Penh at day 2). These comparisons would involve ANOVA analysis presumably since comparing two variables cannot validly be done with t test alone.

4. There should be some discussion of the potential triggers for the tachypnea (e.g., could it be related to neural signals, cytokines, etc.).

5. The most important differences between infants and adults are all presented in Table 1. It might be good to present some of these in figure form also to emphasize the findings that were different between infants and adults (figures 2-5 mostly show findings that did not appear to differ between the groups).

Minor comments
1. The first sentence in paragraph 2 page 2 is not complete.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

no competing interests