PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Does comorbidity increase the risk of mortality among children under 3 years of age?
AUTHORS	Fischer Walker, Christa; Perin, Jamie; Liu, Jodi; Katz, Joanne; Tielsch, James; Black, Robert

VERSION 1 - REVIEW

REVIEWER	Schmidt, Wolf-Peter London School of Hygiene & Tropical Medicine
REVIEW RETURNED	12-Jul-2013

GENERAL COMMENTS	General This study attempts to explore the effect of ALRI/diarrhoea co-infection on mortality in two child cohorts from South Asia. This topic is of obvious importance given that ALRI and diarrhoea continue to be the most frequent causes of child death in poor settings. The authors understandably found it difficult to identify suitable datasets that not only include close follow up of children for disease episodes but are also large enough to include sufficient numbers of death due to either condition. The authors identify an over-additive risk due to co-infection but the confidence intervals are wide. Still, I believe that the findings merit publication, also from the methodological perspective. The article may benefit from a more in-depth discussion of the theory of interaction of two infections (see for example Bhavnani D et al. Am J Epidemiol. 2012 Sep 1;176(5):387-95). I am also a bit unsure about how to interpret the interaction between ALRI and diarrhoea. This seems to be a different issue than for example studying the interaction between two diarrhoea pathogens as in the paper I cite above. The authors state that it has been shown that diarrhoea is associated with an increased risk of ALR. Assuming then that diarrhoea may be a cause of ALRI (not unreasonable if diarrhoea is severe, leaving children dehydrated and immune-compromised) how does this causal pathway correspond to interaction between diarrhoea and ALRI as discussed in this manuscript? Can we speak of interaction or over-additive effects if one condition is a cause of the other? Isn't it to be expected if a child has severe diarrhoea and develops ALRI as a result, that then this child may have a higher risk of death than a child that only has diarrhoea without ALRI? In a way ALRI may be regarded as complication of the first disease, diarrhoea. The authors state that exploring the added effect of ALRI and diarrhoea is difficult because of the lack of population based dataset with enough cases. The authors may want to discuss the possibility of designing a hospital based cohort study focussing on children with diarrhoea or ALRI at baseline, followed up to observe whether they develop the other condition and estimate the associated risk of mortality. See for example: Islam SS, Khan MU.. Int J Epidemiol.

	1986;15:116–21.; Sibal A, Patwari AK, Anand VK, Chhabra AK, Chandra D. J Trop Pediatr. 1996;42:64–67.; Mitra AK, Khan MR, Alam AN.. Trans R Soc Trop Med Hyg. 1991;85:685–87. Minor comments: Abstract: 1. I recommend avoiding the term “statistically significant” in line with current epidemiological/public health practice. Focus should be on effect size and CI. I would be happier with a phrase stating something like this: “We found an effect size of X, but the confidence interval was wide indicating low statistical support” or something along these lines. The key is that there is an effect. We are just not very confident whether its a true finding or a false positive. 2. Some non English native speakers (including myself) are a bit unsure what is meant by biweekly. Perhaps avoid that term. 3. I am a bit unsure about this sentence: “the Cox model assumes that the ratio of mortality rates is constant over time. This is not true among children under 5 years of age; mortality rates decline as the child ages.” As the authors state, the Cox model assumes proportional hazard between two groups of children (e.g. those with diarrhoea and those with diarrhoea and ALRI) over time. If child mortality overall declines with age, while the ratio of rates between these groups stays the same (i.e. mortality declines similarly in the two groups but at different levels) then I thought this was not a problem with Cox regression. Perhaps elucidate for an amateur statistician like me. 4. As far as I know, the key feature of Fenn’s at al study was the use of a bivariate probit model. The fact that GEE was used to account for within child clustering may be of lesser relevance in this discussion (again i say this as an amateur statistician). 5. Perhaps mention software and statistical command used.

REVIEWER	Guerrant, Richard University of Virginia, School of Medicine
REVIEW RETURNED	16-Jul-2013

GENERAL COMMENTS	Important and thorough study of 2 large published cohorts with morbidity surveillance and mortality monitoring in Asia, but still too small to show significant increased risk of both diarrhea and pneumonia on mortality. Questions include: 1. was there a correlation of either diarrhea or pneumonia with malnutrition (wt or stunting)? 2. Increased prevalence of comorbidity with increased disease severity warrants more emphasis in abstract and conclusions. 3. Was the increased risk, albeit not significant, in both NNIP-4 and VASIN of additional mortality among children with both diarrhea and ALRI still insignificant if both studies are combined? What if all treatment groups are included? 4. Another potential limitation on the availability of relevant studies is the clear "Hawthorn" or secular trends effects that have been documented to occur with close monitoring of morbidity, even without specific (other) interventions.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Wolf-Peter Schmidt
London School of Hygiene and Tropical Medicine

General
This study attempts to explore the effect of ALRI/diarrhoea co-infection on mortality in two child cohorts from South Asia. This topic is of obvious importance given that ALRI and diarrhoea continue to be the most frequent causes of child death in poor settings. The authors understandably found it difficult to identify suitable datasets that not only include close follow up of children for disease episodes but are also large enough to include sufficient numbers of death due to either condition. The authors identify an over-additive risk due to co-infection but the confidence intervals are wide. Still, I believe that the findings merit publication, also from the methodological perspective.

The article may benefit from a more in-depth discussion of the theory of interaction of two infections (see for example Bhavnani D et al. Am J Epidemiol. 2012 Sep 1;176(5):387-95).

We agree with the reviewer that the theory of interaction could be explored more and reviewed the articles (and others) to help explain this further. We included the added comment in the discussion section of the paper.

I am also a bit unsure about how to interpret the interaction between ALRI and diarrhoea. This seems to be a different issue than for example studying the interaction between two diarrhoea pathogens as in the paper I cite above. The authors state that it has been shown that diarrhoea is associated with an increased risk of ALR. Assuming then that diarrhoea may be a cause of ALRI (not unreasonable if diarrhoea is severe, leaving children dehydrated and immune-compromised) how does this causal pathway correspond to interaction between diarrhoea and ALRI as discussed in this manuscript? Can we speak of interaction or over-additive effects if one condition is a cause of the other? Isn't it to be expected if a child has severe diarrhoea and develops ALRI as a result, that then this child may have a higher risk of death than a child that only has diarrhoea without ALRI? In a way ALRI may be regarded as complication of the first disease, diarrhoea.

The authors state that exploring the added effect of ALRI and diarrhoea is difficult because of the lack of population based dataset with enough cases. The authors may want to discuss the possibility of designing a hospital based cohort study focussing on children with diarrhoea or ALRI at baseline, followed up to observe whether they develop the other condition and estimate the associated risk of mortality. See for example: Islam SS, Khan MU.. Int J Epidemiol. 1986;15:116–21.; Sibal A, Patwari AK, Anand VK, Chhabra AK, Chandra D. J Trop Pediatr. 1996;42:64–67.; Mitra AK, Khan MR, Alam AN.. Trans R Soc Trop Med Hyg. 1991;85:685–87.

We tried to address these issues in the discussion section. Please see added paragraph on mechanisms.

Minor comments:
Abstract:
1. I recommend avoiding the term "statistically significant" in line with current epidemiological/public health practice. Focus should be on effect size and CI. I would be happier with a phrase stating something like this: "We found an effect size of X, but the confidence interval was wide indicating low statistical support" or something along these lines. The key is that there is an effect. We are just not very confident whether its a true finding or a false positive.
We agree and have adjusted the terminology accordingly.

2. Some non English native speakers (including myself) are a bit unsure what is meant by biweekly. Perhaps avoid that term.

We agree and have adjusted the terminology accordingly.

3. I am a bit unsure about this sentence: “the Cox model assumes that the ratio of mortality rates is constant over time. This is not true among children under 5 years
of age; mortality rates decline as the child ages.” As the authors state, the Cox model assumes proportional hazard between two groups of children (e.g. those with diarrhoea and those with diarrhoea and ALRI) over time. If child mortality overall declines with age, while the ratio of rates between these groups stays the same (i.e. mortality declines similarly in the two groups but at different levels) then I thought this was not a problem with Cox regression. Perhaps elucidate for an amateur statistician like me.
Yes we agree with the reviewer that child age in our model does not preclude Cox regression, however we felt Aalen regression was more appropriate. We have edited the methods section with details about our choice.

4. As far as I know, the key feature of Fenn’s at al study was the use of a bivariate probit model. The fact that GEE was used to account for within child clustering may be of lesser relevance in this discussion (again i say this as an amateur statistician).
We feel Fenn’s mortality analysis is relevant and have chosen to leave this reference in the manuscript. We mentioned Fenn et al’s analysis because they also analyzed comorbidity and its effect on mortality, although their methods were different. Their GEE analysis of mortality was in the same paper, but separate from the bivariate probit model, which was used to analyze morbidity outcomes.

5. Perhaps mention software and statistical command used.
We have included a note in the manuscript about the software used.

Reviewer: RL Guerrant
Center for Global Health
UVa School of Medicine
Charlottesville, VA

Important and thorough study of 2 large published cohorts with morbidity surveillance and mortality monitoring in Asia, but still too small to show significant increased risk of both diarrhea and pneumonia on mortality. Questions include:
1. was there a correlation of either diarrhea or pneumonia with malnutrition (wt or stunting)?
Yes, we agree this may have been useful, but unfortunately neither study collected this information.

2. Increased prevalence of comorbidity with increased disease severity warrants more emphasis in abstract and conclusions.
We added a paragraph on mechanisms that touches on this but also feel this is covered in our previously published paper that was more suited to this topic.

3. Was the increased risk, albeit not significant, in both NNIP-4 and VASIN of additional mortality among children with both diarrhea and ALRI still insignificant if both studies are combined? What if all treatment groups are included?
We included only the iron and placebo arms from the NNIPS-4 study. Children receiving zinc were excluded because the zinc supplementation had a direct impact on mortality. From VASIN, we included both vitamin A and placebo arms of the study. While vitamin A supplemented children did have lower mortality rates, supplementation is now routine in parts of the world with vitamin A deficiency; thus, combining the two groups likely represents a more typical child population with variable vitamin A status and supplementation coverage. For both studies, we conducted the analysis first stratified by treatment groups within each study (i.e., iron vs. placebo for NNIPS-4 and vitamin A

vs. placebo for VASIN) and combined where no difference in the effect of comorbidity on mortality risk was observed between groups.

We did consider combining the studies but when we did this the model no longer represents the data well. Given the small number of deaths in both studies and the example power analysis we present in the discussion, we know that combining would not be adequate to see a statistically significant effect. For these reasons we chose to present both independently.

4. Another potential limitation on the availability of relevant studies is the clear "Hawthorn" or secular trends effects that have been documented to occur with close monitoring of morbidity, even without specific (other) interventions.

We agree that the Hawthorn effect could be decreasing the proportion of episodes that become severe by increasing prompt care seeking for signs and symptoms. We added this idea to the discussion.