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Title	Deprivation and pediatric respiratory tract infection mortality: a cohort study in three high-income jurisdictions
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Reviewer 1	Michael Denis Seear
Institution	Dept. of Pediatrics/ICU, British Columbia Children's Hospital
General comments (author response in bold)	<p>We would like to thank Reviewer 1 for their critical feedback, which has contributed greatly to the general rigor of the paper, but specifically our introduction and discussion sections.</p> <p>1. Difficulty in saying something new about health determinants. In the 50 yrs since the first Whitehall study, the social determinants of health have been picked clean. Those determinants are known so well that it is hard for teams to find something new to add. The authors' justification for their work is "It is unclear whether socio-economic disparities still play a role after birth characteristics have been taken into account." I would suggest that there is already clear agreement on that point and little need for further study. Adverse determinants throughout childhood, are known to have a clear effect on health - both morbidity and mortality. In fact the authors answer the question later on by quoting references 6 and 7. I could add several others. Whether you look at pneumonia mortality or outcomes from chronic diseases, the main adverse risk factors are already known. Poverty is always at the top of the list but some of the others change with region. For example, place of residence is significant in USA but not in British Columbia. The current fashion has been to move on to studying the underlying causes of those determinants but that can't be addressed by this work.</p> <p>The authors agree that the literature on the social determinants of health is increasingly rich; however, in contrast to adult populations, relatively less research has been focused on these factors within high-income, pediatric populations. We have reworded the opening sentence of the abstract to more accurately describe the knowledge gap that this study intended to fill. Much of the work in this field to date has drawn from observations in a single jurisdiction. In the majority of cases where observations have been taken from multiple jurisdictions, these studies have only been able to superficially investigate the impacts of the social determinants of health; e.g., by taking ecological approaches, relying on small sample sizes, etc. The major strength of this study is our ability to carry out analyses in parallel which have leveraged comparable, population-based sources of health administrative data from three similar high-income, English-speaking jurisdictions with comparable healthcare systems, e.g., universal coverage of most primary and acute care services. This has allowed us to demonstrate how, even within generally comparable jurisdictions, local context can influence the social determinant of health a great deal – a nuisance that cross-jurisdictional studies are rarely able to offer.</p> <p>For example, we observed teenage motherhood to be an independent risk factor for RTI-related mortality only in Ontario. This may potentially be due to the relatively infrequency; heightened social stigma; unique correlations between teenage motherhood and other social determinants, particularly being an Indigenous woman; and lack of social supports for teenage mothers in Ontario, which may not be comparable to the experience of</p>

teenage mothers in the other two jurisdictions (England and Scotland). Thus, this work provides motivation for readers to give pause and consider the generalizability of international work to their local contexts, as the magnitude, mechanisms and relative importance of specific social factors may differ between even generally comparable regions, such as those studied herein.

2. In order to make this paper more relevant for pediatricians, my suggestion would be to expand upon the first sentence in the Background paragraph: "Deaths from respiratory tract infections are amenable to public health and medical interventions." That is true for pneumonia and also for most other pediatric diseases. I would emphasise the value of intervention rather than just concluding that further study is needed. In particular, I would slant the discussion towards the relatively new trend for social needs screening at clinic level. At risk children should be identified and given social work support. This work could be seen as supporting that trend.

The authors agree that this would indeed be a valuable addition to the discussion and have incorporated these points. (p. 3)

3. Accuracy of data base studies.

Data base studies have the advantage of examining very large numbers; such studies are now common. However, I find that the large numbers sometimes obscure lack of precision. This study is no different. The study's main measured end point is a good example. Inaccuracy in death certificates is well known. Was the chest infection just one other factor listed on the death certificate or was it actually the single cause of the death? This is not at all clear and no attempt was made to differentiate association from cause even though this was the main outcome measure.

Because RTIs are likely to be variably coded in administrative health databases, we purposefully chose a broad definition of RTI-related deaths to reduce under-estimation of deaths attributable to RTI causes. This allowed for a more sensitive, albeit less specific, ascertainment of deaths associated with RTIs. Notably, most cause of death studies are limited to investigating only those causes identified on the death certificate. One of the strengths of leveraging multi-linked health administrative data is our ability to draw from not only the causes of death listed on the child's death certificate, but also identify RTI-related deaths, i.e., deaths occurring within 30 days of an RTI-related hospital admission. Notably, these deaths would have otherwise been missed by traditional cause-of-death ascertainment methods. There is considerable debate as to whether a single cause can be assigned to death, or whether such practice is indeed appropriate given the multiple of component causes that contribute to most health outcomes. For example, would the death of an infant with chronic lung disease (CLD) who contracted respiratory syncytial virus (RSV) and died, most acutely, as the result of pneumonia most appropriately be contributed to pneumonia, RSV, or the underlying CLD that increased their risk of airway inflammation and an adverse RSV-related outcome? Instead, we sought to identify all deaths which were RTI-related; i.e., occurring near an RTI-associated hospitalization or otherwise coded as having some relationship to an RTI event. We have sought to clarify this distinction in the definition of our outcome measure. (p. 8)

4. Conclusions were drawn by comparing outcomes in Ontario, Scotland and England but the study used three different measures of social deprivation. How can these reasonably be compared? The measures differed in content and also in their basic definition of a census area. In Ontario this was only a few hundred people but the Scottish measure was based on a postal code area of 5,000 people; can these be compared? The three regions may well be modern democratic prosperous areas but they are far from directly comparable. There are numerous problems with direct comparisons and numerous explanations for any observed differences. The issue of first Nations' poverty is unique to Ontario. I don't know about England or Scotland but it wouldn't be hard to find glaring differences at the population level. All these have a bearing on interpreting the final results. Comparing mortality rates against a measure of deprivation is difficult when different measures of deprivation are used and it is not clear whether the pneumonia was really the single cause of mortality.

We appreciate the difficulty in identifying comparable measures of social deprivation across jurisdictions. Most studies are limited to studying area-level income or education as a measure of social deprivation, which are known to have unique issues; e.g. income does not adequately reflect wealth, a more meaningful measure of social status. Instead, we leveraged three comparable measures of social deprivation, which are multidimensional constructs of social deprivation. While each of these measures were developed within their local context and include slightly differing constructs, the comparison of relative ranks within these jurisdictions holds value. We have compared those in the top and bottom 20% of deprivation to each other within each jurisdiction; thus, allowing for the relative comparison of each jurisdiction's most and least deprived infants. While the composition of the populations within each of these groups will indeed be unique across jurisdictions, their relative standing in their broader societies is comparable. As for the variable area size used to calculate each of these area-level measures, we agree that this is a limitation of the study which has likely dampened our ability to accurately assign social deprivation status to unique geographic regions. As mentioned in our discussion section, this has likely led to a more conservative estimate of social differences in the regions based on larger area measures; i.e., Scotland. (p. 14-15)

5. The references appear to be unfinished. refs 1, 3 and 17 are incomplete which calls into question the accuracy of the others.

We greatly appreciate your highlighting this oversight which assumedly happened while switching between the referencing software used by the two research teams. We have revised the references accordingly. (p. 19-21)

6. There are obviously variations with district but, on a global level, pneumonia and diarrhea have been the commonest causes of death in children, outside the perinatal period, since some attempt at accurate numbers was first attempted. The WHO /UNICEF intervention against diarrhea was more successful than the pneumonia control program so pneumonia has been top of the list for at least 30 years. It is well worth studying and treating.

The authors agree.

7. The tables are a bit daunting and could be relegated to the appendix.

The authors appreciate the recommendation and have made edits to

	hopefully make the tables more reader friendly. (tables)
Reviewer 2	Sharon Daniel
Institution	Department of Public Health, Ben-Gurion University, Beer-Sheva, Israel
General comments (author response in bold)	<p>The authors would like to thank Reviewer 2 for their detailed feedback, which has greatly contributed to the clarity and readability of the revised manuscript.</p> <p>1. The authors state that "there is mounting evidence to suggest that socioeconomic disparities may also be distal causes of these clinical factors". In its current form, in my opinion, the study does not add much to the existing literature. A significant contribution that can make a real difference in improving intervention and prevention must assess the risk of specific socio-economic characteristics on RTI death (in other words- which particular characteristics of low socioeconomic status contribute to mortality?). I suggest that the small-area level deprivation scales in every state, if possible, would be broken down to the specific indicators, and the link of every indicator with RTI mortality would be assessed separately.</p> <p>Much of the work in this field to date has drawn from observations in a single jurisdiction. In the majority of cases where observations have been taken from multiple jurisdictions, these studies have only been able to superficially investigate the impacts of the social determinants of health; e.g., by taking ecological approaches, relying on small sample sizes, etc. The major strength of this study is our ability to carry out analyses in parallel which have leveraged comparable, population-based sources of health administrative data from three similar high-income, English-speaking jurisdictions with comparable healthcare systems, e.g., universal coverage of most primary and acute care services. This has allowed us to demonstrate how, even within generally comparable jurisdictions, local context can influence the social determinant of health a great deal – a nuisance that cross-jurisdictional studies are rarely able to offer.</p> <p>For example, we observed teenage motherhood to be an independent risk factor for RTI-related mortality only in Ontario. This may potentially be due to the relatively infrequency; heightened social stigma; unique correlations between teenage motherhood and other social determinants, particularly being an Indigenous woman; and lack of social supports for teenage mothers in Ontario, which may not be comparable to the experience of teenage mothers in the other two jurisdictions (England and Scotland). Thus, this work provides motivation for readers to give pause and consider the generalizability of international work to their local contexts, as the magnitude, mechanisms and relative importance of specific social factors may differ between even generally comparable regions, such as those studied herein.</p> <p>Given that each construct of material deprivation includes slightly different components, we would be unable to conduct a cross-jurisdictional comparison of each of these components. Further, taken on their own, the unique impact of these dimensions would be exceedingly difficult to understand. For example, the Scottish Carstairs Index considers the proportion of residents owning a car; even if available in other jurisdictions, this measure would have differing interpretation – a large proportion of the Ontario population lives in dense, urban communities where car ownership is not necessary. Most studies in this area have been limited to studying</p>

area-level income or education as a measure of social deprivation, which are known to have unique issues; e.g. income does not adequately reflect wealth, a more meaningful measure of social status. Instead, we believe a strength of our study is our ability to leverage three comparable measures of social deprivation, which are multidimensional constructs of social deprivation. While each of these measures were developed within their local context and include slightly differing constructs, the comparison of relative ranks within these jurisdictions holds more meaningful value than the comparison of their component constructs. We have compared those in the top and bottom 20% of deprivation to each other within each jurisdiction; thus, allowing for the relative comparison of each jurisdiction's most and least deprived infants. While the composition of the populations within each of these groups will indeed be unique across jurisdictions, their relative standing in their broader societies is comparable.

2. Rout of administration and risk factors for infection differ between the different pathogens (pertussis, RSV, lobar pneumonia). Therefore, analysis of the specific causes of mortality (according to icd9 codes) is indicated.

Because specific RTI pathogens are variably coded in administrative health databases, laboratory data for confirmed diagnoses are not readably available in all jurisdictions and testing practices substantially vary across jurisdictions (e.g., testing for viral agents is not generally recommended in Ontario due to its limited impact on treatment), we purposefully chose a broad definition of RTI-related deaths to reduce under-estimation of deaths attributable to specific RTI pathogens. This allowed for a more sensitive, albeit less specific, ascertainment of deaths associated with RTIs. We agree that the specific, detailed risk factors for these pathogens differ; however, the medical complexity and timely access to healthcare, as likely driven by socioeconomic and clinical characteristics, are overarching risks factors for all severe RTI-related illnesses. (p. 8)

3. RSV passive vaccinations to neonates and children with chronic diseases, children's pneumococcal and pertussis vaccines, and maternal pertussis vaccines have an enormous influence on the risk of infection. Do the databases contain this data? This should be addressed in the analysis and in the discussion. In addition, please elaborate briefly in the introduction on the vaccination policy and on adherence to vaccinations in all three states.

Unfortunately, this information is not comprehensively available in all of these jurisdictions. We agree that this is an important consideration and have added to our discussion of our study limitations. We have also provided regional level details regarding the availability, coverage and funding of these programs in each jurisdiction as an appendix. To more readily provide the reader with these details, we have provided a brief overview in-text. (Appendix and p.14)

4. Introduction: please elaborate on other known risk and preventive factors for RTI (vaccination including young-adults and maternal vaccinations, hand washing etc.)

We appreciate this suggestion and have provided additional details. (p. 5)

5. Methods, line 129: this is a retrospective cohort study, hence the children were not followed during the study period. please correct throughout the manuscript.

We appreciate this suggestion and have revised our wording accordingly. (p. 7)

6. Results: second paragraph including tables 1+2 - please move to the appendix. Report on the rate of total deaths in one or two brief sentences.

We agree this would increase readability and have revised accordingly. (Tables moved to appendix)

7. Figure 3 appears in the text before figure 1.

We appreciate your catching this error and we have revised.

8. Figure 3- please report the p values for all log-rank tests in the figures or/and in the text.

Thank you for highlighting this omission, we will add these values to the figure. (Please note these values are pending)

9. Figure 1+2: the report on HRs for the reference groups (HR=1) is unnecessary.

We agree and have revised accordingly. (Please note these values are pending) (Figure)

10. Please report the mean survival and the p values for survival until RTI mortality in the text.

We appreciate you highlighting this omission and we will report median survival time by jurisdiction. (p. 11)

11. Cox regression- How was the assumption of proportionality assessed? please elaborate.

We appreciate you raising this omission and have added appropriate details to our methods and result sections. The proportionality of hazards between deprivation groups was assessed by inspecting Nelson Aalen Plots. (p. 10 and p. 12)