Author's response to reviews

Title: Contribution of respiratory tract infections to child deaths: a data linkage study

Authors:

Pia Hardelid (p.hardelid@ucl.ac.uk)
Nirupa Dattani (n.dattani.1@city.ac.uk)
Mario Cortina-Borja (m.cortina@ucl.ac.uk)
Ruth Gilbert (r.gilbert@ucl.ac.uk)

Version: 4
Date: 7 October 2014

Author's response to reviews: see over
Dear Dr. Muscatello,

Thank you for your email of the 25th September, inviting us to resubmit our paper. We are grateful to the reviewers for their comments, and have addressed these point-by-point below. The revised manuscript is also attached. All changes have been made in response to reviewers’ comments or to correct minor typos.

Thank you again for considering our paper for publication in BMC Public Health. We look forward to hearing from you.

Yours sincerely,

Pia Hardelid

(On behalf of all authors)
Reviewer's report 1

Reviewer's report:

Thanks you for asking me to review this paper.

Major Compulsory Revisions

1) The assumption concerning winter excess of RTI related deaths might not be entirely valid. The assumption (line 125) states: "We assumed that the winter excess of RTI-related deaths could potentially be prevented through prompt identification and treatment, universal vaccination strategies with effective vaccines or improved hygiene measures such as handwashing." An equally valid assumption would be that indoor social activity in winter months contributed to excess RTI-related deaths. But noone would therefore suggest living outdoors in the winter months. In other words, a proportion of winter-excess deaths are NOT preventable. Moreover, if the assumption was that universal vaccination strategies could be adopted to reduce excess RTI-related deaths, why was this not specifically tested. It is entirely possible, although not investigated in this study, that the excess deaths occurred in those who had already been vaccinated. These limitations do not diminish the importance of the findings. But they should be mentioned in the Discussion and the overall findings presented more cautiously. Any implication that ALL excess RTI-related deaths in winter are preventable should be avoided.

We agree with the reviewer that the assumption for excess deaths may have been too strongly worded. We have now amended this in the methods section to say that some of these deaths may be preventable through measures such as treatment or vaccination. In the discussion, we have now also spelled out more clearly that it is unlikely that all of these deaths can be prevented, as well as included a sentence regarding RTIs delaying death but not preventing death completely (see point 2 below).

2) Similarly, although the thrust of the article quite rightly was on the potential for preventing RTI-related death, the majority of deaths occurred in children with Neuro conditions. And they have to die of something. So RTI probably represents an end-point of neurological (usually cerebral palsy etc) debility. If you successfully treat/prevent the RTI, it will surely only return after a few months of further progressive neurological decline. This issue of 'deferred death' rather than 'prevented death' should be discussed.

We agree with the reviewer that this is an important point. Such a 'harvesting' effect has not been well studied in children however. We have now included a statement regarding this issue in the discussion.

3) The issue of Flu, Pneumococcal vaccination and potential RSV vaccination in children is not clearly discussed. The authors merely conclude, 'However, evidence is needed on the effectiveness of these preventive programmes in practice'. The authors have identified and defined the categories of child death which involved RTIs. They have implied preventability based on winter excess. But what about reasonable estimates of the preventability that could be attributable to RSV, Flu and Pneumococcal vaccination programmes (and in those with an without LTCs). Even a ball-park figure would give a context to the data - and there are several references which could be used to supply estimates (although I grant you that these are very rough estimates for this population).
As the reviewer points out, there is little evidence of effectiveness of either influenza vaccine, palivizumab (for RSV) or pneumococcal vaccine effectiveness in children with chronic conditions, particularly not for preventing deaths. We have however expanded the discussion on page 8 to state the effectiveness of these various interventions, although still pointing out that the evidence base for these interventions for preventing deaths in children with chronic conditions is highly limited.

Minor Essential Revisions
1) Abstract: I think it would help to clarify the statement 'These deaths declined by 2.3% per year in infants......'. Firstly, the word 'these' is ambiguous and the sentence would be clearer if it began: 'In infants aged 28-364 days,......'. Secondly, the rate of decline in deaths is described as 2.3% per year. Is this 2.3% per year, year on year (i.e. a reduction of well over 23% over the 10 years, based on the effect of cumulative reductions of 2.3%)? Or is it a total of 23% reduction over 10 years?

The 2.3% comes from the Poisson regression model (it is the exponential of the model coefficient for year). Since the model is fitted on a log scale, it means that the total decline is compounded over the years so that the total decline is greater than \(10^{*2.3}\). In fact the total decline between the rate in 2001 (30.1/100000 pop) and the rate in 2010 (21.4/100,000 pop) is 28.9%. We have now clarified in the results section that the 2.3% comes from a statistical model and we now also state the total % decline between 2001 and 2010.

2) Introduction, para 1. The authors correctly cite the literature for deaths from pneumococcal infections prior to introduction of the pneumococcal vaccine in 2006. Why no reference to deaths since then (data are available)?

We have now amended this sentence to include a more recent estimate from van Hoek et al (2012) of 17 deaths per year due to invasive pneumococcal disease in young children (aged <5 years) in 2009/10.

3) The Methods used by the authors in obtaining records are excellent. They did well to identify 14180 hospital records of the 22509 deaths. They should discuss in the Limitations section that records for the remaining one third of child deaths will be in primary care, may have contained data on RTIs, but were not included in this study. In practice, these data are not available and until the HSCIC issues with care.data are resolved, no researchers have national access to patient-level primary care data. Nevertheless, this should be stated as a Limitation.

We agree with the reviewers that linkage to primary care databases is likely to identify further children who had an RTI but have not had a hospital admission in the last month before death. In addition, more severely ill children may have received care in hospices, and may have had an RTI whilst cared for in a hospice setting which may have been missed on death certificates. We have now included a section in the discussion regarding extending linkage to primary care and hospice databases.

4) The justification for the authors’ Method comes in the Results. Had they confined their analysis to Death Certs alone, they would have merely identified 3339 child deaths attributable to RTIs. Using linked hospital records, they identified 5039 child deaths with codings for RTIs. The authors could make more of this finding of another ~1700 RTI-related deaths identified by case-note searches. It is mentioned in the Discussion, Pg6 Line 215, but not the fact that this yielded almost 50% additional cases.
We have now included a sentence in the discussion highlighting the large number of extra cases that we could identify through linkage.

5) A key finding is the change in RTIs over the 10-year study period. I could not see the actual figures. The authors display the data in Figure 1. See comment about Abstract above - it was unclear whether the key finding of 2.3% reduction each year (children aged 1 month to 1 year) referred to a cumulative reduction of 2.3% every year which over 10 years would add up to considerably more than 23%. To clarify, it would be more helpful if the authors summarised the TOTAL 10-year reduction in % in this age cohort.

This has now been clarified – please see the response to query 1.

6) Looking at the Supplementary Files, I thought Table S2 should be discussed further (in the Discussion). How does it happen that a sizeable proportion of children dying in hospital, have no record of an RTI in their case-notes and yet RTI appears on the Death Cert?

Table S2 shows agreement in recording of any respiratory condition (not just RTIs) in the proportion of children who died during and outside a hospital admission. As the reviewer rightly points out, 15% of children who died in hospital had a respiratory condition recorded on their death certificate but not on a hospital record within 30 days of death. One reason for this might be that a respiratory condition had been in the patients’ hospital notes but not entered on HES (for example, if the diagnosis was not considered to alter the tariff received by the hospital). Also, since our key aim was to examine the role of acute RTIs in child deaths, we did not consider RTIs or other respiratory conditions recorded in hospital records during episodes which started more than 30 days before death. In these cases, respiratory conditions may have been recorded in earlier episodes during longer hospital stays or during earlier hospital admissions.

We have now amended the manuscript to raise the issue of relatively poor agreement between hospital records and death certificates in the results section (also in response to the second reviewer’s comments) on page 5 as well as in the discussion, with reference to previous studies in this area.

Reviewer’s report 2

Reviewer’s report: Thank you for the opportunity to review an interesting research. The authors explored RTI-mortality rates in a large population of children. Strengths of the work include large sample size, data linkages for validation purposes, and use of administrative data for clinical diagnosis. As the authors acknowledge, the limited agreement between hospital records and death certificate data regarding RTI-related death definition represents a major weakness of the current manuscript. I have several minor comments that the authors may wish to address.

1) Abstract
Methods section: you may wish to mention data source for analysis
We now clarify that we use death certificates linked to longitudinal hospital records in this study.

Methods:
2) The classification of winter and summer periods is questionable, and the authors may wish to use a different term (difficult to see how April or May or September can be considered winter months). Did the authors have information on other children's characteristics, ie birthweight, pre-term birth, parents social class, BMI? These factors may be of relevance to the estimation models.
We chose this period to define winter and summer as it is the period used for respiratory infection surveillance in England, the rest of the UK and Europe (as specified in reference 19). We appreciate that this may not have been very clear and have now spelled this out in the methods section.

We agree with the reviewer that these are key variables which we would have liked to consider in the analyses. Information on BMI is not recorded in HES. Obesity is included as one of the metabolic/endocrine chronic conditions, provided the ICD-10 code had been entered and coded in HES. (See reference 14). As we point out in the discussion, we could not look at mortality rates according to chronic conditions (as we did not have appropriate denominators).

Parents’ (usually the father’s) social class are entered on death records of children, however unfortunately we did not have access to this data. For children born before April 1997 (the financial year from which it is possible to link records to persons in HES), information on birthweight, gestational age etc is not available. For children born in and after April 1997, this information is available through the HES maternity tail for some hospitals (see Murray et al, J Public Health, 2013). In the third paragraph in the discussion, we raise the possibility of creating birth cohorts using longitudinal linkage of hospital records to further examine risk factors for RTI-related mortality. We have now expanded this part of the discussion to also include some of the risk factors raised by the reviewer.

3) The source of hospital admissions data is not made clear ie HES? Data cleaning procedures?
We have now clarified that we used HES as the source of the linked hospital records and inserted a reference for this data source in the methods section. Data cleaning procedures are described in detail elsewhere – please see reference 14.

4) What about antibiotics prescribing?
Although we agree this is an important issue, antibiotic (or other) prescribing in hospital is not available through HES, and as pointed out by reviewer 1, we did not have access to primary care records to allow ascertainment of antibiotic prescribing prior to hospital admission. Also, we did not have access to data on children who did not die. We therefore believe the effectiveness of antibiotics in preventing these deaths is outside the remit of the paper. In addition, any such effectiveness study would lead to confounding by indication (since more severely ill children would be more likely to be prescribed antibiotics) which would need to be carefully considered and appropriately addressed. We have now clarified in the methods section that HES does not contain information on hospital prescribing, and included antibiotic prescribing as one of the treatments which may prevent an RTI death in the methods section on page 4.

Results
5) The second paragraphs of the results section is confusing different % of children with RTI on death certificates or hospital records up to 30 days before death are mentioned. What is the correct figure?

There was previously a word missing in this paragraph which made it unclear to readers – this has now been amended. We have now also clarified that the third figure (45.2%) refers to the number of children who have any respiratory condition recorded on either their death certificate or their hospital record up to 30 days before death. That passage now reads:

10169 children (45.2%) had at least one respiratory condition (including RTIs and other respiratory conditions) listed on their death certificates or on hospital records up to 30 days before death. This was equivalent to 504 RTI-related deaths and 1017 any respiratory condition-related deaths per year respectively.
6) The authors may wish to quantify the agreement score in the text. We have now inserted the agreement score on page 5.

Discussion
7) The authors may wish to discuss how antibiotics prescribing may influence RTI-death in children. As stated our response to query 4), the effectiveness of antibiotics in preventing deaths from RTIs is outside the scope of this paper. We agree with the reviewer that antibiotics are an extremely important intervention to prevent or delay death, and have therefore mentioned antibiotics as one of the treatments which may prevent an RTI death in the methods section on page 4. We have also included a discussion of the role of antibiotics in delaying, rather than preventing death, in response to point 2) made by reviewer 1.

8) Could chronic condition therapy influence RTI onset and progression?

This is an important point, however this is likely to differ according to the type of chronic condition. With asthma for example, evidence is mixed regarding whether different combinations of corticosteroids can prevent exacerbations (see for example Johnston et al, Journal of Allergy and Clinical Immunology, 2005, and Mackenzie et al, Clinical and Experimental Allergy, 2013). 64% of children who died with an RTI in this study had a neurological condition. Some of these children are likely to require invasive ventilation to allow them to breathe which may lead to pneumonia (see for example Zhu et al 2014). We therefore feel that a full discussion of this topic is outside the scope of the paper. We have however inserted a sentence regarding improved care for chronic conditions as one of the pathways through which deaths from RTIs could potentially be prevented (on page 4).