BMJ Open

Risk factors associated with RSV hospitalisation in the first 2 years of life, among different subgroups of children in NSW: a whole-of-population-based cohort study

Nusrat Homaira,[1] Kylie-Ann Mallitt,[1] Ju-Lee Oei,[1,2] Lisa Hilder,[1,3] Barbara Bajuk,[4] Kei Lui,[1] William Rawlinson,[5,6,7] Tom Snelling,[8,9,10] Adam Jaffe[1,11]

To cite: Homaira N, Mallitt K-A, Oei J-L, *et al*. Risk factors associated with RSV hospitalisation in the first 2 years of life, among different subgroups of children in NSW: a whole-of-population-based cohort study. *BMJ Open* 2016;**6**: e011398. doi:10.1136/bmjopen-2016-011398

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-011398).

Received 5 February 2016
Revised 19 May 2016
Accepted 7 June 2016

For numbered affiliations see end of article.

Correspondence to
Dr Nusrat Homaira; n.homaira@unsw.edu.au

ABSTRACT

Background: Data on risk factors for respiratory syncytial virus (RSV)-associated hospitalisation in Australian children may be informative for preventive measures.

Methods: A whole-of-population-based study was conducted to identify comparable risk factors for RSV hospitalisation in different subgroups of children aged <2 years in New South Wales. The cohort was divided into Indigenous children and high-risk and standard risk non-Indigenous children. Data on risk factors were obtained from the Perinatal Data Collection. RSV hospitalisations were ascertained from the Admitted Patient Data Collection. Adjusted HRs were calculated for each subgroup. Population-attributable risk associated with risk factors was estimated.

Results: Four factors were associated with increased risk of RSV hospitalisation: maternal smoking during pregnancy, male sex, multiparity and birth during the first half of the RSV season. Increase in relative socioeconomic advantage was associated with decreased risk of hospitalisation. Among high and standard risk non-Indigenous children, the hazard was approximately double for children born to multiparous women compared to those born to primiparous women and among Indigenous children the hazard was approximately double among those born during the first half of the RSV season. Maternal smoking during pregnancy was associated with a 26–45% increased risk across subgroups and accounted for 17% (95% CI 9.3% to 24%) of RSV hospitalisations in Indigenous children, 5% (95% CI 2.5% to 8%) in high-risk and 6% (95% 5% to 7%) in standard risk non-Indigenous children.

Discussion: Promoting avoidance of smoking during pregnancy may help in lowering the disease burden, with Indigenous children likely to benefit most.

Strengths and limitations of this study

- This was a large retrospective cohort study comprising of whole-of-population of children aged <2 years born in New South Wales (NSW) between 2001–2010, which enabled investigation of important risk factors associated with respiratory syncytial virus (RSV) hospitalisation among specific subgroups of children including Indigenous children, high-risk children and standard risk children.
- To the best of our knowledge, this study, for the first time, provided estimation of population attributable risk associated with risk factors for RSV hospitalisation, which may help policymakers in prioritising areas for public health interventions.
- The study used routinely collected data, and lacked information relating to a few risk factors for RSV hospitalisation. However, several surrogate variables were constructed to better capture this missing information.
- The study also relied on RSV coded hospitalisation, as RSV is not routinely tested in NSW, which may have led to underestimation of RSV-related hospitalisation.

INTRODUCTION

Background

Globally, acute lower respiratory infections (ALRIs) are a major cause of childhood morbidity and mortality.[1] Respiratory syncytial virus (RSV) continues to be the major viral cause of hospitalisation for childhood ALRIs. Studies have reported young age, premature birth, male sex, children with bronchopulmonary dysplasia (BPD), birth during the RSV season, day care attendance and household crowding as some of the significant risk factors for severe RSV disease in children.[2–6]

While several studies have looked into the risk factors associated with severe childhood RSV-ALRIs, most have not examined the risk factors at a whole-of-population level over an

extended time frame.[3–5 7] Many studies have only focused on risk factors within specific high-risk populations of interest individually, such as preterm children, children with BPD or native American children,[3–5 8–10] and are therefore limited for comparing the importance of risk factors of children at high-risk with those of standard risk children. Furthermore, data on risk factors from Australian children are limited. A case–control study from Townsville, Queensland, in a sample of 271 children aged <3 years, showed that birth weight <2500 g, maternal parity and marital status were independent predictors for RSV hospitalisation.[11] However, this information does not provide subgroup-specific risk factors.[11]

Objectives

In our previous study on a cohort of children born in New South Wales (NSW), Australia, we demonstrated that the burden of RSV hospitalisation was exceptionally high among Indigenous children and among children who were born preterm or with BPD.[12] The rate/1000 child-years associated with RSV hospitalisation for this cohort of children aged <5 years was 11.0 for Indigenous children, 81.5 for children with BPD, 10.2 for preterm children with gestational age (GA) 32–36 weeks, 27.0 for children with GA 28–31 weeks, 39.0 for children with GA <28 weeks and 4.9 for all other children. Each episode of RSV hospitalisation was associated with a mean cost of $A9190 for Indigenous children, $A12 731 for children with BPD and $A9354 for preterm children.[12] For this study, our objective was to identify those risk factors—for the same cohort—that were similar in different subgroups of children with high rates of RSV hospitalisation and in the general population, which may help in making policy decisions regarding investing in interventions to reduce the disease burden across all groups of children. In addition, we also estimated the population-attributable risk (PAR) associated with the comparable risk factors that may be targeted for public health interventions. While assessment of risk factors for a specific population of interest provides information for developing targeted intervention, it is limited in the sense that it does not provide information regarding the potential impact on the disease burden by removing a specific set of risk factors. PAR gives an estimate of the amount of disease that can be reduced by eliminating the risk factor/s of interest and measures the proportion of cases that can be attributed to a given risk factor at the population level.

METHODS

Study design

The study was a retrospective cohort analysis involving analyses of population-based linked administrative data. The Centre for Health Record Linkage (http://www.cherel.org.au) in NSW conducts linkage of various administrative health data sets for the purpose of research. The linkage process has been described in detail previously.[12]

Study site

The study was conducted in NSW, and comprised all children who were born in NSW from 1 January 2001 to 31 December 2010. The cohort was identified from the NSW Perinatal Data Collection (PDC), which registers all births in NSW. This data set also provided information on maternal, perinatal and sociodemographic risk factors. The Admitted Patient Data Collection (APDC) provided information regarding all RSV hospitalisations in the study birth cohort. Children born with BPD and born at gestational age <31 weeks requiring NICU admission were identified from the Neonatal Intensive Care Units' (NICUS) Data Collection.

Study participants

As our previous analyses from this cohort and other studies suggest that the rate of RSV hospitalisation decreased markedly after age 2 years,[12 13] we only included children up to age 2 years in this analysis. Each child was followed from birth until he or she turned 2 years old, or until the end of the follow-up period (31 December 2010), or death, whichever was earlier. In addition, based on findings from our previous analyses,[12] we divided the cohort into three subgroups:

1. Indigenous children: children of mothers whose Indigenous status was recorded as Aboriginal and/or Torres Strait Islander in any of the data sets were considered to be Indigenous, including any born preterm, or born with low birth weight or with BPD.
2. Non-Indigenous high-risk children: non-Indigenous children who (i) were born preterm (GA <37 weeks), (ii) were born at term with a birth weight of <2500 g or (iii) had BPD.
3. Non-Indigenous standard risk children: all other non-Indigenous term children.

Variables

Exposure variables

Maternal risk factors included were age at birth of the cohort child, smoking status during pregnancy (yes/no), multiparity (previous pregnancies lasting >20 weeks or first birth used as a surrogate measure for having elder siblings at home; yes/no) and index of socioeconomic disadvantage of the mother's residential postcode at birth.

We also included child factors: sex, plurality of birth (multiple birth or singleton; yes/no), mode of delivery (normal vaginal delivery; yes/no), need for oxygen supplementation at birth (yes/no) and birth during the first half of RSV season (yes/no, born between 1 April and 30 June or not, as the RSV season in NSW is generally between April and September).

Outcome variable

The outcome variable of interest was any episode of RSV-coded hospitalisation in the cohort child in the first

2 years of life. The International Classification of Diseases, 10th edition (ICD-10), primary diagnostic codes were used to identify RSV hospitalisations. All hospitalisations coded as RSV pneumonia (J12.1), acute RSV bronchitis (J20.5) and acute RSV bronchiolitis (J21.0) were included as RSV hospitalisations.

Data sources

The data relating to the exposure variables were retrieved from the PDC. The corresponding hospitalisation history/outcome variable for each cohort child identified in the PDC was collected from the linked APDC. Socioeconomic disadvantage was measured using the SEIFA (Socioeconomic index of areas) Indices of Relative Socioeconomic Advantage and Disadvantage (IRSAD) from the Australian Bureau of Statistics.[14]

Bias

This was a large whole-of-population-based study with minimum selection bias. We used only RSV-coded hospitalisations and not laboratory confirmed RSV hospitalisation, which may have led to underestimation of number of events. RSV is not routinely tested in NSW, which does not allow estimation of laboratory confirmed RSV-associated hospitalisation at a population level. Furthermore, our previous analysis from this cohort[12] has shown that all the RSV-coded hospitalisations were recorded during the RSV season, so it is likely that we captured the majority of episodes of RSV hospitalisations in this cohort.

Study size

This was a whole-of-population study including all children born in NSW between 2001 and 2010, so we did not perform any sample size calculation for our study.

Quantitative variables

Maternal age at birth of the cohort child was divided into five age groups including age <20 years, 20–24 years, 25–29 years, 30–34 years and ≥35 years, where age group 25–29 years was considered as the referent group. IRSAD was divided into quintiles from least to most advantaged, where level one was most disadvantaged (referent group) and level five was most advantaged.[14]

Statistical analyses

Assessment of risk factors

This was a cohort study where children were followed from birth, and the association between RSV hospitalisation and various risk factors was determined using hazard analyses taking the age of the child at hospitalisation as the relevant time to event. As we had data for the whole population, followed over time, hazard analysis was chosen as the preferred method for statistical analysis.[15] Univariate analyses of each of the exposure variables were undertaken after checking whether proportional hazard assumptions were valid. Only variables with a p value of ≤0.2 were included in the full multivariable model. We used backward elimination retaining only variables with p value <0.05 in the final model. Separate models were constructed for each of the predefined subgroup of children. In the adjusted model, we also explored for two-way interactions between significant variables, using a likelihood ratio test. Explanatory variables with missing data were Indigenous status of the mother, maternal age at birth of the child, maternal smoking during pregnancy, plural birth and socioeconomic disadvantage of the area of residence. Oof 1 264 943 observations, there were 7432 (0.5%) observations with one or more variables missing, these were excluded from the final analyses.

Estimation of PARs

We estimated adjusted PARs, which refer to the reduction of disease if all the significant risk factors are eliminated. However, as all risk factors, such as sex of the child or plural birth, can neither be eliminated nor controlled, we also estimated the partial PAR, which measured the PAR for the risk factors associated with RSV hospitalisation that can be targeted for public health interventions after adjusting for other variables.[16] PARs for each risk factor and their 95% CIs were estimated from the adjusted HR and the observed prevalence of the risk factor in the study cohort, using a user-friendly publicly available SAS macro (http://www.hsph.harvard.edu/faculty/spiegelman/par.html).

RESULTS

Profile of the cohort

The cohort comprised of 866 262 children, 2295 (0.3%) of whom died while hospitalised during the follow-up period. Almost one-quarter of the mothers of the children of Indigenous origin were aged <25 years compared to around 18% in the high-risk and 16% in the standard risk groups. A total of 51% of mothers of Indigenous children, 20% of high-risk children and 12% of standard risk children smoked during pregnancy (table 1).

Risk factors for RSV hospitalisation

In the adjusted multivariable model (table 2), there were four factors associated with increased risk of RSV hospitalisation across all subgroups of children: maternal smoking during pregnancy, multiparity of the mother, being a male child and being born during the first half of the RSV season. Among high-risk and standard risk non-Indigenous children, the hazard was approximately double for children born to multiparous women and among Indigenous children the hazard was approximately double among those who were born during the first half of the RSV season compared with those who were not. Maternal smoking during pregnancy was associated with a 26–45% increased risk of RSV-hospitalisations.

Increasing socioeconomic advantage was associated with lower risk of RSV hospitalisation across the three

Table 1 Distribution of sociodemographic and perinatal factors in children aged <2 years in NSW: 2001–2010

Sociodemographic and perinatal factors	Indigenous children N=26 523 (3%)	Non-Indigenous high-risk children N=66 172 (8%)	Non-Indigenous standard risk children N=773 567 (89%)
Maternal age (%) (years)			
<20	5272 (20)	2561 (4)	25 767 (3)
20–24	8521 (32)	8928 (13.5)	103 400 (13)
25–29	6303 (24)	17 165 (26)	214 906 (28)
30–34	4143 (15)	21 299 (32)	261 272 (34)
≥35	2284 (9)	16 219 (24)	168 222 (22)
Maternal smoking during pregnancy (%)	13 592 (51)	13 013 (20)	91 037 (12)
Multiparity of the mothers (%)	17 655 (67)	34 386 (52)	450 809 (58)
Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) (%)			
1 (most disadvantaged)	4160 (16)	5432 (8)	57 066 (7)
2	6 437 (24)	8057 (12)	91 727 (12)
3	9534 (36)	15 035 (23)	170 317 (22)
4	5095 (19)	18 288 (28)	207 032 (27)
5 (most advantaged)	1286 (5)	19 316 (29)	246 938 (32)
Male sex (%)	13 839 (52)	33 597 (51)	398 011 (51)
Plural birth (%)	630 (2)	13 890 (21)	9944 (1)
Normal vaginal birth (%)	18 689 (70)	30 195 (46)	474 979 (61)
Requiring oxygen therapy after birth (%)	4266 (16)	15 705 (24)	99 996 (13)
Born during the first half of the RSV season (%)	6613 (25)	16 510 (25)	190 900 (25)
Total number of RSV hospitalisations (% of all RSV hospitalisations in the cohort)	1129 (7)	2389 (15)	12 062 (77)

NSW, New South Wales; RSV, respiratory syncytial virus.

subgroups of children. For high-risk and standard risk non-Indigenous children, each unit increase in IRSAD quintile (compared to the most disadvantaged group) was associated with a 10–30% decrease in risk of hospitalisation. Compared to Indigenous children in the most disadvantaged group, the risk for Indigenous children in the second and third quintile decreased by 25%, but was not significantly different between the most disadvantaged and most advantaged groups.

Non-Indigenous high-risk and standard risk children born to mothers aged >29 years had a 10–30% lower risk of RSV hospitalisation compared to those born to mothers aged 25–29 years; the risk increased in these groups of children born to mothers aged <20 years compared to those aged 25–29 years. The risk of RSV hospitalisation among Indigenous children did not vary significantly by maternal age at birth (table 2).

In the adjusted model, we investigated interactions between children born during the first half of the RSV season, and multiparity. Among non-Indigenous standard risk children, the relative hazard associated with birth during the first half of the RSV season compared to at other times was higher for children born to multiparous women than for those who were firstborn or for those who were not born during the first half of the RSV season (table 2).

Population attributable risk

The adjusted PAR associated with all significant risk factors among Indigenous, non-Indigenous high-risk and standard risk children were 62% (95% CI 56% to 67%), 70% (95% CI 56% to 81%) and 90% (95% CI 87% to 92%), respectively (table 3).

DISCUSSION

Our study provides comprehensive population level data from an Australian cohort on risk factors for RSV hospitalisation across different subgroups of children at high-risk. This study identified five major risk factors common to all the groups of children including maternal smoking during pregnancy, multiparity of the mother, male sex of the child, birth during the first half of the RSV season and low relative socioeconomic disadvantage. These risk factors have been shown to be important in other populations as well.[2 3] Though there are specific alleles in genes associated with innate immunity that are associated with severe RSV disease in different subgroups,[18] the findings of our study suggest that certain risk factors associated with severe RSV diseases are similar for all subgroups of children. This also suggests that interventions targeted towards these specific risk factors may be beneficial for all children.

The analysis was based on routinely collected administrative data, so we lacked information regarding some potentially important risk factors such as breastfeeding, household crowding, day care attendance and family history of allergies.[19] However, our study identified various important risk factors and it is unlikely that the other unidentified risk factors would have nullified the association observed in this study. We did not have

Table 2 HR for RSV-associated hospitalisation in children aged <2 years in NSW

Exposures	Indigenous children	Non-Indigenous high-risk children	Non-Indigenous standard risk children
Unadjusted HR (95% CI)			
Maternal age (years)			
<20	0.97 (0.78 to 1.20)	0.92 (0.71 to 1.18)	1.30 (1.18 to 1.44)
20–24	1.01 (0.83 to 1.21)	1.10 (0.71 to 1.18)	1.25 (1.18 to 1.39)
25–29	Referent group[17]		
30–34	0.96 (0.76 to 1.21)	0.85 (0.76 to 0.96)	0.90 (0.86 to 0.95)
≥35	0.77 (0.57 to 1.05)	0.86 (0.75 to 0.97)	0.822 (0.77 to 0.87)
Maternal smoking during pregnancy	1.42 (1.23 to 1.65)	1.46 (1.29 to 1.59)	1.75 (1.66 to 1.83)
Multiparity of the mother	1.38 (1.18 to 1.63)	1.96 (1.78 to 2.16)	2.19 (2.09 to 2.29)
IRSAD			
1 (most disadvantaged)	Referent group[17]		
2	0.73 (0.58 to 0.91)	0.72 (0.60 to 0.87)	0.82 (0.76 to 0.89)
3	0.72 (0.58 to 0.88)	0.73 (0.62 to 0.86)	0.86 (0.80 to 0.93)
4	0.80 (0.55 to 1.15)	0.70 (0.60 to 0.83)	0.76 (0.70 to 0.81)
5 (most advantaged)	0.82 (0.56 to 1.2)	0.61 (0.52 to 0.72)	0.66 (0.62 to 0.71)
Male sex	1.2 (1.07 to 1.42)	1.17 (1.07 to 1.28)	1.35 (1.29 to 1.40)
Plural birth	1.05 (0.64 to 1.73)	1.17 (1.05 to 1.30)	1.50 (1.38 to 1.73)
Normal vaginal birth	0.95 (0.81 to 1.11)	0.92 (0.84 to 1.01)	1.13 (1.09 to 1.18)
Requiring oxygen therapy after birth	1.03 (0.89 to 1.24)	1.16 (1.04 to 1.28)	1.07 (1.01 to 1.14)
Born during the first half of the RSV season	1.65 (1.42 to 1.91)	1.29 (1.17 to 1.42)	1.52 (1.46 to 1.58)
*Adjusted HR (95% CI)**			
Maternal age (years)			
<20		1.15 (0.89 to 1.49)	1.70 (1.54 to 1.89)
20–24		1.16 (1.00 to 1.34)	1.30 (1.23 to 1.38)
25–29	Referent group		
30–34		0.81 (0.72 to 0.92)	0.84 (0.80 to 0.89)
≥35		0.77 (0.67 to 0.88)	0.71 (0.67 to 0.75)
Maternal smoking during pregnancy†	**1.39 (1.20 to 1.61)**	**1.26 (1.13 to 1.41)**	**1.47 (1.40 to 1.55)**
Multiparity of the mother†	**1.35 (1.15 to 1.59)**	**2.07 (1.87 to 2.30)**	**2.36 (2.23 to 2.50)**
IRSAD†			
1 (most disadvantaged)	Referent group		
2	0.75 (0.60 to 0.94)	0.71 (0.59 to 0.86)	0.84 (0.77 to 0.91)
3	0.75 (0.61 to 0.92)	0.72 (0.61 to 0.85)	0.89 (0.83 to 0.96)
4	1.02 (0.81 to 1.27)	0.77 (0.65 to 0.90)	0.87 (0.81 to 0.94)
5 (most advantaged)	0.91 (0.63 to 1.32)	0.74 (0.63 to 0.88)	0.88 (0.82 to 0.95)
Male sex†	**1.24 (1.07 to 1.43)**	**1.19 (1.08 to 1.30)**	**1.34 (1.29 to 1.40)**
Plural birth		1.20 (1.07 to 1.35)	1.47 (1.28 to 1.70)
Normal vaginal birth		0.87 (0.79 to 0.96)	0.90 (0.87 to 0.94)
Requiring oxygen therapy after birth		1.14 (1.03 to 1.27)	1.08 (1.03 to 1.15)
Born during the first half of the RSV season†	**1.63 (1.41 to 1.90)**	**1.30 (1.18 to 1.44)**	**1.35 (1.24 to 1.47)**
Birth during the first half of RSV season X multiparity of the mother			1.17 (1.06 to 1.28)

*Only factors that remained significant in the adjusted model are presented and factors that were significant for all the three subgroups of children are in bold.
†Factors with a p value <0.05 across all the subgroups in the adjusted model.
IRSAD, Indices of Relative Socioeconomic Advantage and Disadvantage; NSW, New South Wales; RSV, respiratory syncytial virus.

access to innate factors that may put children at higher risk, nevertheless, the primary objective of the study was to identify comparable risk factors across different subgroups of children, which can be targeted for public health interventions. We used the summary of the socioeconomic disadvantage index of the area of residence of the mother and had no individual level information on parental education nor on household income; information that may have provided a more accurate measure of socioeconomic disadvantage. As there is no routine testing of RSV performed in NSW, it was not possible for us to confirm the RSV coded hospitalisations, which might have led to underestimation.

Maternal smoking, which is a directly modifiable factor, was one of the most important risk factors associated with an increased risk of RSV hospitalisation in our cohort. Although we did not have data on household exposure to smoke and maternal smoking after

Table 3 Partial population-attributable risk for risk factors associated with RSV hospitalisation in children aged <2 years in NSW

Risk factors	Indigenous children	Non-Indigenous high-risk children	Non-Indigenous standard risk children
Partial PAR (95% CI)			
Maternal smoking	17% (9.3% to 24%)	5% (2.5% to 8%)	6% (5% to 7%)
Birth during the first half of the RSV season	14% (9% to 18%)	7% (4% to 10%)	9% (6.5% to 11%)
Multiparity of the mother	19% (9% to 29%)	35% (30% to 40%)	44% (41% to 45%)

NSW, New South Wales; PAR, population-attributable risk; RSV, respiratory syncytial virus.

pregnancy—which might have confounded the impact of maternal smoking during pregnancy—the evidence for passive exposure to smoking and maternal smoking in general is not universally established.[2] On the other hand, maternal smoking during pregnancy has been identified as a significant risk factor for RSV hospitalisation in a number of studies.[3 4] It is believed that maternal smoking during pregnancy alters the lung morphology of the fetus in utero, leading to reduced lung function in infants,[20] with a subsequent increase in risk of developing severe RSV disease. The prevalence of maternal smoking during pregnancy was particularly high (51%) among Indigenous mothers, which is known to be a major contributing factor to disparities in health and well-being. The prevalence was also unacceptably high (12–20%) for mothers in other groups, given the known deleterious effect of maternal smoking on the child's respiratory health.[21] We estimated that eliminating maternal smoking during pregnancy could reduce RSV hospitalisation by 7–25%, a reduction that would yield greatest benefit for Indigenous children. The success of public health interventions promoting cessation of maternal smoking during pregnancy will, however, be dependent on persistence of cessation beyond the pregnancy period.

The cohort children born during the first half of the RSV season were at significantly higher risk of RSV hospitalisation. Our previous analyses of this cohort have shown that the rate of RSV hospitalisation was highest for children aged <6 months.[12] This has been a consistent finding for RSV hospitalisation.[2 7] A possible explanation is that infants born during the first half of the RSV season are likely to have greater exposure to circulating RSV at an age when they are most vulnerable. These children might also be born with reduced levels of maternal anti-RSV antibody compared to the levels in children born after the RSV season.[2 22] Children born to multiparous women also had higher risk of RSV hospitalisation compared with those born to primiparous women; this is presumably because multiparity is a strong surrogate for having one or more older children at home. Other studies have suggested that having day-care centre/school going siblings[2 5 23 24] or having more children at home[8] is associated with severe disease. The increased risk of young children with older siblings is most likely related to greater exposure to high viral loads resulting from enhanced interpersonal transmission.[2] The findings imply that preventive measures targeted towards children who have older siblings at home may help in lowering the disease burden. Indeed, research findings suggest that promoting hand hygiene in homes with young children can reduce within-household transmission of respiratory illness.[25]

Though the risk of RSV hospitalisation decreased with increasing levels of socioeconomic advantage compared with most disadvantaged group for standard-risk and high-risk children, the risk did not vary for Indigenous children in the fourth and fifth quintile compared to that of the least disadvantaged quintile. One possible explanation is that only 24% of the Indigenous children were in the highest two quintiles and the greatest burden of the disease was in the lowest three quintiles. In addition, increasing maternal age did not decrease the risk of RSV hospitalisation in Indigenous children. The interplay of sociodemographic factors in the Indigenous population is much more complex. Younger Indigenous mothers are more likely to represent the lowest quintile of the SEIFA index and, regardless of maternal age and socioeconomic index, other factors of social inequalities prevalent in the Indigenous population including inadequate and inequitable literacy rate and limited access to healthcare[26] may confound the effect of maternal age on RSV hospitalisation in this group of children.

The findings of the study have several important policy implications. Although there is no effective vaccine against RSV yet available, palivizumab, a humanised prophylactic antibody, can significantly reduce the burden of severe disease in high-risk children.[27 28] As our previous analyses have shown that Indigenous children and high-risk children are likely to be hospitalised more frequently due to RSV,[12] those children who are aged <6 months during the RSV season or who have older siblings at home may be considered for prophylactic administration of palivizumab. When an effective RSV vaccine becomes available, passive immunisation for all children aged <6 months through maternal immunisation may protect the very young children through the first RSV season. In the mean time, efforts to reduce RSV disease burden will be dependent on promoting hand hygiene among young children, to reduce within-household transmission, and also on avoidance of maternal smoking during pregnancy.

Author affiliations
[1]Discipline of Paediatrics, Faculty of Medicine, School of Women's and Children's Health, UNSW Australia, Sydney, New South Wales, Australia
[2]Department of Newborn Care, Royal Hospital for Women, Randwick, New South Wales, Australia
[3]National Perinatal Epidemiology & Statistics Unit, Centre for Big Data Research in Health UNSW Australia, Sydney, New South Wales, Australia
[4]NSW Pregnancy and Newborn Services Network, Sydney Children's Hospitals Network, Westmead, New South Wales, Australia
[5]Serology and Virology Division, SEALS Microbiology, Prince of Wales Hospital, Randwick, New South Wales, Australia
[6]School of Medical Sciences, UNSW Australia, New South Wales, Australia
[7]School of Biotechnology and Biomolecular Sciences, UNSW Australia, New South Wales, Australia
[8]Princess Margaret Hospital, Perth, Western Australia, Australia
[9]Wesfarmers Centre of Vaccines & Infectious Diseases, Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia
[10]Menzies School of Health Research and Charles Darwin University, Darwin, Australia
[11]Respiratory Department, Sydney Children's Hospital, Randwick, New South Wales, Australia

Acknowledgements The authors are grateful to the staff members of the Respiratory Department of Sydney Children's Hospital, Randwick and Virology Research Laboratory of Prince of Wales Hospital, Randwick, for their cooperation. The authors thank the Directors, the NICUS members and the audit officers of all tertiary units in supporting this collaborative study: NICUS, Dr Jennifer Bowen (Chairperson), Barbara Bajuk (Coordinator), Sara Sedgley (Research Officer); Canberra Hospital, Dr Hazel Carlisle (Director), Professor Alison Kent, Judith Smith; John Hunter Children's Hospital, Dr Paul Craven (Director), Lynne Cruden, Alissa Argomand; Royal Prince Alfred Hospital, Ingrid Rieger (Director), Dr Girvan Malcolm, Tracey Lutz (Clinical Director), Shelley Reid; Liverpool Hospital, Dr Jacqueline Stack (Director), Dr Ian Callander, Kathryn Medlin, Kaye Marcin; Nepean Hospital, Dr Vijay Shingde, Mee Fong Chin, Kerrie Bonzer; The Children's Hospital at Westmead, Professor Nadia Badawi (Director), Dr Robert Halliday, Caroline Karskens; Royal North Shore Hospital, Dr Mary Paradisis (Director), A/Prof Martin Kluckow, Claire Jacobs; Sydney Children's Hospital, Dr Andrew Numa (Director), Dr Gary Williams, Janelle Young; Westmead Hospital, Dr Melissa Luig (Director), Jane Baird; and Royal Hospital for Women, A/Professor Kei Lui (Director), Dr Ju-Lee Oei, Diane Cameron. The authors also thank the babies and their families, and the nursing and midwifery, obstetric and medical records staff of the obstetric and children's hospitals in NSW, and the ACT.

Contributors NH, AJ, TS and WR conceived and designed the study. NH was responsible for analysing and drafting the manuscript. K-AM contributed expertise in the development of the statistical analysis plan for the study. KO, J-LO, LH and BB provided technical feedback with design, analyses and drafting of the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Ethics approval NSW Population and Health Service Research (HREC/09/CIPHS/33; 2009/05/155), and the Aboriginal Health and Medical Research Council Ethics (726/10) committees.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This study used linked administrative data of all children born in NSW between 2001 and 2010. These data are available to researchers on request and subject to approval from the relevant data custodians and ethics committees, and via linkage conducted by the NSW Centre for Health Record Linkage (http://www.cherel.org.au).

REFERENCES

1. Nair H, Simoes EA, Rudan I, *et al*. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* 2013;381:1380–90.
2. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr* 2003;143:S118–26.
3. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jimenez J, *et al*. FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. *Pediatr Infect Dis J* 2008;27:788–93.
4. Figueras-Aloy J, Carbonell-Estrany X, Quero J. Case–control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33–35 weeks in Spain. *Pediatr Infect Dis J* 2004;23:815–20.
5. Liese JG, Grill E, Fischer B, *et al*. Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany. *Eur J Pediatr* 2003;162:230–6.
6. Law BJ, Carbonell-Estrany X, Simoes EA. An update on respiratory syncytial virus epidemiology: a developed country perspective. *Respir Med* 2002;96(Suppl B):S1–7.
7. Papenburg J, Hamelin ME, Ouhoummane N, *et al*. Comparison of risk factors for human metapneumovirus and respiratory syncytial virus disease severity in young children. *J Infect Dis* 2012;206:178–89.
8. Bulkow LR, Singleton RJ, Karron RA, *et al*. Risk factors for severe respiratory syncytial virus infection among Alaska native children. *Pediatrics* 2002;109:210–16.
9. Bockova J, O'Brien KL, Oski J, *et al*. Respiratory syncytial virus infection in Navajo and White Mountain Apache children. *Pediatrics* 2002;110:e20.
10. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. *Pediatrics* 1988;82:199–203.
11. Reeve CA, Whitehall JS, Buettner PG, *et al*. Predicting respiratory syncytial virus hospitalisation in Australian children. *J Paediatr Child Health* 2006;42:248–52.
12. Homaira N, Oei JL, Mallitt KA, *et al*. High burden of RSV hospitalization in very young children: a data linkage study. *Epidemiol Infect* 2016;144:1612–21.
13. Nielsen HE, Siersma V, Andersen S, *et al*. Respiratory syncytial virus infection—risk factors for hospital admission: a case–control study. *Acta Paediatr* 2003;92:1314–21.
14. Smithers LG, Searle AK, Chittleborough CR, *et al*. A whole-of-population study of term and post-term gestational age at birth and children's development. *BJOG* 2015;122:1303–11.
15. Samet JM, Muñoz A. Evolution of the cohort study. *Epidemiol Rev* 1998;20:1–14.
16. Wand H, Spiegelman D, Law M, *et al*. Estimating population attributable risk for hepatitis C seroconversion in injecting drug users in Australia: implications for prevention policy and planning. *Addiction* 2009;104:2049–56.
17. Malacova E, Li J, Blair E, *et al*. Neighbourhood socioeconomic status and maternal factors at birth as moderators of the association between birth characteristics and school attainment: a population study of children attending government schools in Western Australia. *J Epidemiol Community Health* 2009;63:842–9.
18. Janssen R, Bont L, Siezen CLE, *et al*. Genetic susceptibility to respiratory syncytial virus bronchiolitis is predominantly associated with innate immune genes. *J Infect Dis* 2007;196:826–34.
19. Anderson LJ, Parker RA, Strikas RA, *et al*. Day-care center attendance and hospitalization for lower respiratory tract illness. *Pediatrics* 1988;82:300–8.
20. Hanrahan JP, Tager IB, Segal MR, *et al*. The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992;145:1129–35.
21. Cook DG, Strachan DP. Health effects of passive smoking-10: summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999;54:357–66.
22. Glezen WP, Paredes A, Allison JE, *et al*. Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group, and maternal antibody level. *J Pediatr* 1981;98:708–15.
23. Carbonell-Estrany X, Quero J, Bustos G, *et al*. Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a prospective study. IRIS Study Group. *Pediatr Infect Dis J* 2000;19:592–7.
24. Carbonell-Estrany X, Quero J, Group IS. Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons. *Pediatr Infect Dis J* 2001;20:874–9.

25. Lee GM, Salomon JA, Friedman JF, *et al*. Illness transmission in the home: a possible role for alcohol-based hand gels. *Pediatrics* 2005;115:852–60.
26. Hodyl NA, Grzeskowiak LE, Stark MJ, *et al*. The impact of Aboriginal status, cigarette smoking and smoking cessation on perinatal outcomes in South Australia. *Med J Aust* 2014;201:274–8.
27. Resch B. Palivizumab in preventing respiratory syncytial virus-related hospitalization in high-risk infants. *Expert Rev Pharmacoecon Outcomes Res* 2008;8:529–38.
28. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;102(3 Pt 1):531–7.