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RSV INCREASES THE RISK OF FIRST EPISODE OF SEVERE ASTHMA IN DIFFERENT SUB-GROUPS OF CHILDREN AT RISK: A WHOLE-OF-POPULATION STUDY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017936
Article Type:	Research
Date Submitted by the Author:	29-May-2017
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology, Infectious diseases, Respiratory medicine
Keywords:	RSV, Asthma, Cohort study

RSV INCREASES THE RISK OF FIRST EPISODE OF SEVERE ASTHMA IN DIFFERENT SUB-GROUPS OF CHILDREN AT RISK: A WHOLE-OF-POPULATION STUDY

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Running title: RSV and risk of first asthma hospitalization

Key words: RSV, asthma, cohort study

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ABSTRACT

Objective: To determine the contribution of respiratory syncytial virus (RSV) to subsequent development of asthma in different sub-groups of children at risk of severe RSV disease.

Settings: The study was conducted in NSW, Australia

Participants: The study comprised all children born in NSW between January 1st 2000 and December 31st 2010. Each child was included from birth through the end of the follow up period (31 December 2010). The cohort was divided in to three sub-groups:

1. Non-Indigenous high-risk children: Non-Indigenous children born preterm or born with a low birth weight.

2. Indigenous children: Children of mothers whose Indigenous status was recorded as Aboriginal and/or Torres Strait Islander.

3. Non-Indigenous standard risk children: All other non-Indigenous term children.

Primary outcome measure: Risk of development of severe asthma in different sub-groups of children who had RSV hospitalization in the first two years of life compared to those who did not.

Design: We performed a retrospective cohort analysis using population-based linked administrative data. Extended Cox model was used to determine hazard ratio (HR) and 95% confidence interval (CI) around the HR for first asthma hospitalization in different sub-groups of children.

Results: The cohort comprised 847,516 children born between 2000-2010. In the adjusted Cox model, the hazard of first asthma hospitalization was higher and comparable across all sub-groups of children who had RSV hospitalization compared to those who did not. The HR (95% CI) was highest in children aged 2-3 years; 4.3 (95% CI 3.8-4.9) for high-risk, 4.0 (95% CI 3.3-4.8) for Indigenous and 3.9 (95% CI 3.7-4.1) for non-Indigenous standard risk children. This risk persisted beyond seven years of age.

Conclusion: This large study confirms a comparable increased risk of first asthma hospitalization following RSV disease in the first two years of life across different sub-groups children at risk.

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Strengths and Limitations:

- To our knowledge this is the first study to demonstrate increased risk of first asthma hospitalization following severe RSV disease concurrently in different sub-groups of high-risk children at a population level.
- The study cohort comprised of all chidlren born in NSW between 2000-2010 which enabled us to determine the risk of asthma in different age-groups extending beyond seven years.
- This was an epidemiological study using linked administrative data and lacked information relating to factors like atopic predisposition and risk of subsequent asthma in this cohort, hence a causal association cannot be established for RSV hospitalization.

INTRODUCTION

Background:

Globally, acute lower respiratory infections (ALRIs) are a major cause of childhood morbidity and mortality [1]. Early life respiratory viral infections have been linked to the development of subsequent asthma in children [2]. This link has been particularly highlighted for early respiratory syncytial virus (RSV) infection in children which continues to be the major viral cause of childhood ALRIs in the first two years of life[3]. It has been proposed that severe RSV infection in early childhood is associated with impaired lung function which persists beyond childhood and increases risk of recurrent wheezing and asthma at a later age of life[4 5]. Asthma symptoms associated with severe RSV illness in first year of life can even persist in early adulthood [6]. In addition early RSV hospitalization may also result in reduced lung function, even in the absence of asthma symptoms [6]. Although there is some evidence that severe RSV disease and allergic sensitisation may be linked via interleukin (IL)-13/IL-4 gene polymorphisms, severe RSV infection in early childhood is possibly a consequence rather than a cause of a predisposition to severe reversible airway diseases [7 8].

Objectives

Australia has a high prevalence of paediatric asthma compared to other developed countries [9 10]. It is estimated that 21% of Australian children aged 0 to 15 years have had a previous diagnosis of asthma, with 11% having a current diagnosis of asthma [11]. In 2014, more than 13,000 children aged 1–17 years presented to New South Wales (NSW) emergency departments for asthma, representing two-thirds of all hospital presentations across the state and yielding a significant burden on the health care system [12]. The burden of RSV-associated LRTI is also very high in NSW, especially in children aged <2 years with an average annual direct health care cost of more than AUD nine million in NSW alone[13]. In addition, our previous study has demonstrated that the incidence of severe RSV disease

was exceptionally high among children who were born preterm or with broncho-pulmonary dysplasia (BPD) and Indigenous children of NSW [13] . It is, therefore, important to determine what, if any, contribution early severe RSV disease has on subsequent asthma hospitalizations in these sub-groups of children at risk. While data exist on the high burden of RSV disease in these sub-groups of children, to our knowledge, no study has investigated the contribution of RSV to subsequent asthma risk in different high-risk paediatric populations simultaneously. Such information will be important to inform targeted public health interventions aimed to lower the burden of severe asthma in Australian children.

To address this knowledge gap, we conducted a retrospective population-based cohort study designed to investigate the role of early RSV ALRI on the subsequent risk of development of severe asthma in different sub-groups of children at risk in NSW.

METHODS:

Study Design:

The study was a retrospective cohort analyses using linked population based administrative data.

Study site & study population:

The study was conducted in NSW, Australia comprising all children who were born in NSW between January 1st 2000 and December 31st 2010. Each child was included from birth through the end of the follow up period (31 December 2010) or in-hospital death, whichever was earlier. The birth cohort was divided in to three sub-groups:

1. Non-Indigenous high-risk children: Non-Indigenous children who 1) were born preterm (gestational age (GA) <37 weeks), 2) were born at term with a birth weight of <2500 grams

2. 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.

3. Non-Indigenous standard risk children: All other non-Indigenous term children.

Variables:

Exposure variables:

The main exposure variable of interest was any episode of RSV coded hospitalization in the cohort child from birth to two years of age, the peak age-group for RSV hospitalizations[13]. The International Classification of Diseases, 10th edition (ICD-10) primary diagnostic codes were used to identify RSV hospitalizations. Any hospitalization with primary diagnostic codes associated with RSV pneumonia (J12.1), acute RSV bronchitis (J20.5), acute RSV bronchiolitis (J21.0), unspecified acute lower respiratory infections (J22), unspecified acute bronchitis (J20.9) and unspecified acute bronchiolitis (J21.9) identified during RSV season (April-September in NSW) were included as RSV hospitalizations.

Outcome variable:

The outcome variable of interest was first episode of asthma hospitalization beyond the age two years until the end of follow up. All hospitalizations with primary diagnostic codes associated with asthma (J45), predominantly allergic asthma (J45.0), non-allergic asthma (J45.1), mixed asthma (J45.8), asthma unspecified (J45.9) and status asthmaticus (J46) or wheeze (R0.62) were considered as asthma hospitalizations.

Confounders:

Confounders included in the analysis were based on the published literature and included maternal and child factors [14]. Maternal variables were age at birth of the cohort child, parity, smoking during pregnancy and index of socio-economic disadvantage of the mother's residential postcode at birth. Child factors included in the analyses were season of birth and sex of the child.

Data sources:

The Centre for Health Record Linkage (CHeReL) (www.cherel.org.au) in NSW conducts linkage of various administrative health data sets for research purposes. CHeReL follows best practice probabilistic linkage [15] to combine personal information to produce a person-based dataset using the NSW Perinatal data Collection as the primary dataset to which all other datasets are linked. Each child was assigned a Patient Project Number and this was attached to the records in each source database. All other personal identifiers were removed from each of the datasets and the de-identified datasets with the unique identifier key were provided to the study investigators. One of the study investigators (NH) combined records of the same child in the different data sets using the unique identifier key and undertook data cleansing.

The cohort was identified from the NSW Perinatal Data Collection in which all births in NSW are registered. Data relating to any episode of RSV and asthma in the cohort children

were retrieved from the Admitted Patient Data Collection. This data set also contained outcome of each hospitalization including discharge status, death, and need for transfer. The corresponding maternal, perinatal and socio-demographic factors for the cohort children were retrieved from the Perinatal Data Collection which was linked to the Admitted Patient data Collection. Socioeconomic disadvantage based on maternal post code of residence at the time of birth of the cohort child was measured using the SEIFA (Socioeconomic index of areas) Indices of Relative Socioeconomic Advantage and Disadvantage (IRSAD) from the Australian Bureau of Statistics [16].

Bias:

This was a large whole-of-population based cohort study based on almost complete data sets. Out of 1,264,943 observations, there were 7,432 (0.5%) observations with one or more variables missing which were excluded from the final analyses.

Study size:

This was a whole-of-population study including all children born in NSW between 2000-2010 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 <20 years, 20-24 years, 25-29 years, 30-34 years and ≥35 years; 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 and level five was most advantaged and level one was considered as the referent group [16].

Statistical Analyses:

This was a cohort study where children were followed from birth and the risk of subsequent first asthma hospitalization beyond the age of two years was determined using hazard analyses taking age of the child at asthma hospitalization as the relevant time to event.

As the hazard of subsequent asthma hospitalization was non-proportional violating the proportionality hazard assumption of standard Cox model, we used an extended Cox model with time varying covariate to account for the non-proportionality. The age at asthma hospitalization was split in to 2-3 years, 3-5 years, 5-7 years and >7 years age groups and the interaction between baseline RSV risk and subsequent asthma hospitalization was examined for the different age groups. Separate models were constructed for each of the pre-defined sub-group of children. The final multivariable model was adjusted for all available confounders mentioned in the method section. We estimated the hazard ratio (HR) and the 95% Confidence Intervals (CI) around the HR of first asthma hospitalization after the age of two years for children with versus without any RSV hospitalization in their first two years of life.

Ethics approval:

The project was approved by the NSW Population and Health Service Research (HREC/09/CIPHS/33; 2009/05/155) and the Aboriginal Health and Medical Research Council Ethics (726/10).

RESULTS:

Profile of the Cohort:

The cohort comprised 847,516 children born between 2000-2010. Of these, 437,034 (52%) were male and the mean age of the cohort at the end of the follow up period was 73 months (SD±42 months) (Table 1). In total 31,831 (4%) cohort children had at least one episode of RSV hospitalization before the age of two years, of which 2,405 (7.5%) also had an episode asthma hospitalization after the age of two. The median age at first asthma hospitalization was 3.2 years (IQR 2.5-4.4 years).

Table 1: Perinatal and socio-demographic characteristics of cohort children born in NSW between 2000-2010

N= 847,516		
Exposures	**Children with RSV hospitalisation in the first two years of life**	**Children without any RSV hospitalisation in the first two years of life**
	n=31,831	n=815,685
	n (% within RSV group)	
Maternal age		
<20 years	2,102 (6)	32,088 (4)
20-24 years	6,342 (19)	113,813 (14)
25-29 years	9,022 (28)	227,139 (28)
30-34 years	9,081 (28)	270,626 (33)
≥35 years	5,284 (17)	172,019 (21)
Maternal smoking during pregnancy	8,178 (26)	112, 584 (14)
Multiparity of the mother	23,211 (73)	470,574 (58)

IRSAD		
1 (most disadvantaged)	4,032 (13)	78,280 (10)
2	4,941 (15)	101,577 (12)
3	8,405 (26)	189,507 (23)
4	7,906 (25)	208,681 (26)
5 (most advantaged)	6,512 (20)	239,566 (29)
Male sex of the baby	18,799 (59)	397,005 (49)
Season of birth		
Summer	8,121 (26)	195,652 (24)
Autumn	10,470 (33)	198,355 (24)
Winter	7,193 (23)	207,579 (25)
Spring	6,047 (19)	214,099 (26)
High-risk children	4,902 (15)	60,637 (7)
Indigenous children	2,960 (9)	26,732 (3)
Non-Indigenous standard risk children	26,172 (82)	741,025 (91)
Asthma hospitalisation beyond age of 2 years	2,405 (7.5)	19,974 (2)

Hazard for asthma hospitalization:

In the adjusted multivariable Cox hazard model, the hazard of first asthma hospitalization persisted to be double beyond the age of seven years for children who were hospitalised with RSV in the first two years of life compared to those who were not (Table 2). The adjusted hazard for first asthma hospitalization was highest for children between the ages 2-3 years. The adjusted HR at ages 2-3 years for non-Indigenous standard risk children was 3.9 (95% CI 3.7-4.1), for high-risk children was 4.3 (95% CI 3.8-4.9) and for Indigenous

children was 4.0 (95% CI 3.3-4.8). The risk of asthma hospitalization at different ages was comparable across the different sub-groups of children.

Table 2: Hazard ratio for first asthma hospitalization beyond the age of two years in different sub-groups of children who had severe RSV disease in the first two years of life compared to those who did not: NSW 2000-2010

Age at first asthma hospitalisation	Non-Indigenous standard risk children		High-risk children		Indigenous children	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
2-3 years	4.1 (3.9, 4.4)	3.9 (3.7, 4.1)	4.7 (4.2, 5.3)	4.5 (4.0, 5.1)	4.1 (3.4, 4.9)	4.0 (3.3, 4.8)
3-5 years	3.0 (2.9, 3.2)	2.8 (2.7, 3.0)	3.1 (2.7, 3.5)	3.0 (2.7, 3.4)	2.2 (1.8, 2.7)	2.2 (1.8, 2.6)
5-7 years	2.4 (2.2, 2.7)	2.3 (2.1, 2.5)	2.6 (2.1, 3.2)	2.6 (2.1, 3.2)	2.6 (1.9, 3.4)	2.5 (1.9, 3.3)
>7 years	2.8 (2.4, 3.2)	2.6 (2.3, 3.0)	3.5 (2.7, 4.5)	3.4 (2.6, 4.3)	2.0 (1.4, 3.1)	1.9 (1.2, 2.9)

** Hazard ratio after adjusting for mother's age at birth of the cohort child, parity, maternal smoking during pregnancy, index of socio-economic disadvantage of the mother's residential postcode at birth, season of birth and sex of the child.*

DISCUSSION:

To our knowledge this is the first study to demonstrate increased risk of first asthma hospitalization following severe RSV disease in different sub-groups of high-risk children concurrently. Our findings are based on a very large population cohort of children followed up to 11 years of age, suggest that different sub-groups of high-risk children, who developed RSV disease within the first two years of life continue to be at elevated risk of first asthma hospitalization beyond the age of seven years. The hazard of first asthma hospitalization was similar across all sub-groups of children with the hazard being four times higher at ages 2-3 years. Although premature children and Indigenous children aged <2 years are at almost 10 times higher risk of acquiring severe RSV disease compared to standard risk children[13], the similar hazard of subsequent asthma hospitalization across different sub-groups of children suggest that RSV might be the strongest predictor for developing subsequent severe childhood asthma. Thus RSV might not only be the main cause for acute respiratory illness but also be an important contributor to chronic respiratory morbidity in children.

The risk of first asthma hospitalization in our cohort children who had severe RSV disease leading to hospitalization in their first two years of life was significantly higher across all the age strata. It is possible that many of the first asthma hospitalization within ages 2-3 and 3-5 years in our analysis may have been due to recurrent wheeze. Indeed diagnosis of asthma in children aged <5 years is challenging. The Global Initiative for Asthma guideline (GINA) suggest that symptoms including frequent episodes of wheeze, activity-induced cough or wheeze, nocturnal cough without viral infections in periods without viral infections which persist beyond three years of age are suggestive of asthma in children <5years of age [17]. In addition RSV disease has been associated with increased risk of persistent wheezing in children [5 18]. However the risk of first asthma hospitalization in this cohort was also significantly higher at ages 5-7 years and beyond seven years of age. Another longitudinal

study done in the UK had also reported that the odds of doctors diagnosed asthma beyond the age of seven was double for children who had RSV hospitalization in the first year of life compared to the those who did not [18]. Other studies have also noted that risk of subsequent asthma following early RSV illness can persist until 11 years of age [5] and even in adulthood [6]. It is believed that early severe lower RSV infection may cause airway remodelling and impair development of the growing lung which persists in later life [19]. Even mild RSV disease may lead to residual impaired lung function in children up to the age of 13 years [5].

A limitation of the study is our outcome variable of interest was coded asthma hospitalization beyond the age of two years. However this was a population based study using administrative data where diagnosis of diseases was based on ICD codes. We did not have access to any information regarding atopic predisposition of children; it is likely that many children hospitalised with asthma were atopic. If early severe RSV disease is also a manifestation of atopic predisposition, it is possible that the observed relationship between RSV and asthma is not causal. However, other studies suggest the association between asthma and RSV is independent of atopic history [20 21]. As this was an epidemiological study causality of the association between RSV and asthma cannot be confirmed, but the findings are comparable to other studies adding to the body of evidence that a strong association exists. We did not have access to ambulatory care data so could not assess the association between less severe forms of RSV infection and asthma not requiring hospitalization. In our cohort there were only 335 hospitalizations coded as associated with any other viral ALRI in the first two years of life, compared with 31,831 RSV-associated ALRI hospitalizations; we therefore did not investigate association between other specific virus- specific ALRI and asthma. This work compliments the apparent association between RSV disease with the subsequent development of asthma [5], while infections with other

viruses like rhino and influenza viruses [22] are more clearly associated with exacerbations of asthma. In addition even if any association exist, their contribution to asthma is likely to be comparatively small.

Our study confirms that hospitalization for severe RSV disease in the first two years of life is associated with the subsequent hospitalization for first episode of asthma hospitalization in Australian children. While there are currently no effective antivirals or vaccines targeting RSV, several vaccines are being evaluated in clinical trials [23]. Once an effective vaccine becomes available, long term follow-up of children to evaluate the impact on subsequent asthma development will help define the causal pathway of RSV and asthma, particularly in the high-risk groups. Meanwhile, more conservative preventive strategies such as frequent hand washing[24] targeted to prevent transmission RSV diseases may also have the added benefit of reducing the burden of asthma in children.

ACKNOWLEDGEMENTS

The authors would like to thank Sydney Children's Hospital foundation and Rotary Club of Sydney Cove for their continued support in our research endeavours. We are grateful to Respiratory Department of Sydney Children's Hospital, Randwick and Virology Research Laboratory of Prince of Wales Hospital, Randwick for their cooperation. We thank the Aboriginal Health and Medical Research Council and Ministry of Health, NSW. We also thank the babies and their families, the nursing and midwifery, obstetric and medical records staff of the obstetric and children's hospitals in NSW and the ACT.

Authors' contribution: NH and AJ conceived and designed the study. NH, NB and CP was responsible for analysing the data. NH drafted the manuscript. TS, WR, KL, J-L O, LH and BB provided technical feedback with design, analyses and drafting of the manuscript.

Competing interest: None declared

Funding: This work was supported by The Rotary Club of Sydney Cove and the Cerebral Palsy Alliance of Australia. The funding organization had no role in the study design, analyses or drafting of the manuscript.

Data sharing statement: This study used linked administrative data. 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). There is no additional data available.

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STROBE Statement—Checklist of items that should be included in ***cohort studies***

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017936.R1
Article Type:	Research
Date Submitted by the Author:	28-Jul-2017
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology, Infectious diseases, Respiratory medicine
Keywords:	RSV, Asthma < THORACIC MEDICINE, Cohort study

RSV INCREASES THE RISK OF FIRST EPISODE OF SEVERE ASTHMA IN DIFFERENT SUB-GROUPS OF HIGH-RISK CHILDREN IN NSW: A WHOLE-OF-POPULATION BASED COHORT STUDY

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Running title: RSV and risk of first asthma hospitalization

Key words: RSV, asthma, cohort study

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ABSTRACT

Objective: To determine the contribution of respiratory syncytial virus (RSV) to the subsequent development of asthma in different sub-groups of children at risk of severe RSV disease.

Settings: The study was conducted in New South Wales (NSW), Australia

Participants: The study comprised all children born in NSW between 2000-2010 with complete follow-up till December 31st 2011. The cohort was divided in to three sub-groups:

1. Non-Indigenous high-risk children: Non-Indigenous children born preterm or born with a low birth weight.

2. Indigenous children: Children of mothers whose Indigenous status was recorded as Aboriginal and/or Torres Strait Islander.

3. Non-Indigenous standard risk children: All other non-Indigenous term children.

Primary outcome measure: Risk of development of severe asthma in different sub-groups of children who had RSV hospitalization in the first two years of life compared to those who did not.

Design: We performed a retrospective cohort analysis using population-based linked administrative data. Extended Cox model was used to determine hazard ratio (HR) and 95% confidence interval (CI) around the HR for first asthma hospitalization in different sub-groups of children.

Results: The cohort comprised 847,516 children born between 2000-2010. In the adjusted Cox model, the hazard of first asthma hospitalization was higher and comparable across all sub-groups of children who had RSV hospitalization compared to those who did not. The HR (95% CI) was highest in children aged 2-3 years; 4.3 (95% CI 3.8-4.9) for high-risk, 4.0 (95% CI 3.3-4.8) for Indigenous and 3.9 (95% CI 3.7-4.1) for non-Indigenous standard risk children. This risk persisted beyond seven years of age.

Conclusion: This large study confirms a comparable increased risk of first asthma hospitalization following RSV disease in the first two years of life across different sub-groups children at risk.

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Strengths and Limitations:

- To our knowledge this is the first study to demonstrate increased risk of first asthma hospitalization following severe RSV disease concurrently in different sub-groups of high-risk children at a population level.
- The study cohort comprised all children born in NSW between 2000-2010 which enabled us to determine the risk of asthma in different age-groups extending beyond seven years.
- This was an epidemiological study using linked administrative data and lacked information relating to factors like atopic predisposition and risk of subsequent asthma in this cohort, hence a causal association cannot be established for RSV hospitalization.

INTRODUCTION

Background:

Globally, acute lower respiratory infections (ALRIs) are a major cause of childhood morbidity and mortality [1]. Early life respiratory viral infections have been linked to the development of subsequent asthma in children [2]. This link has been particularly highlighted for early respiratory syncytial virus (RSV) infection in children which continues to be the major viral cause of childhood ALRIs in the first two years of life[3]. It has been proposed that severe RSV infection in early childhood is associated with impaired lung function which persists beyond childhood and increases risk of recurrent wheezing and asthma at a later age of life[4 5]. Asthma symptoms associated with severe RSV illness in first year of life can even persist in early adulthood [6]. In addition early RSV hospitalization may also result in reduced lung function, even in the absence of asthma symptoms [6]. Although there is some evidence that severe RSV disease and allergic sensitisation may be linked via interleukin (IL)-13/IL-4 gene polymorphisms, severe RSV infection in early childhood is possibly a consequence rather than a cause of a predisposition to severe reversible airway diseases [7 8].

Objectives

Australia has a high prevalence of paediatric asthma compared to other developed countries [9 10]. It is estimated that 21% of Australian children aged 0 to 15 years have had a previous diagnosis of asthma, with 11% having a current diagnosis of asthma [11]. In 2014, more than 13,000 children aged 1–17 years presented to New South Wales (NSW) emergency departments for asthma, representing two-thirds of all hospital presentations across the state and yielding a significant burden on the health care system [12]. The burden of RSV-associated LRTI is also very high in NSW, especially in children aged <2 years with an average annual direct health care cost of more than AUD nine million in NSW alone[13]. In addition, our previous study has demonstrated that the incidence of severe RSV disease

was exceptionally high among children who were born preterm or with broncho-pulmonary dysplasia (BPD) and Indigenous children of NSW [13] . It is, therefore, important to determine what, if any, contribution early severe RSV disease has on subsequent asthma hospitalizations in these sub-groups of children at risk. While data exist on the high burden of RSV disease in these sub-groups of children, to our knowledge, no study has investigated the contribution of RSV to subsequent asthma risk in different high-risk paediatric populations simultaneously. Such information will be important to inform targeted public health interventions aimed to lower the burden of severe asthma in Australian children.

To address this knowledge gap, we conducted a retrospective population-based cohort study designed to investigate the role of early RSV ALRI on the subsequent risk of development of severe asthma in different sub-groups of children at risk in NSW.

METHODS:

Study Design:

The study was a retrospective cohort analyses using linked population based administrative data.

Study site & study population:

The study was conducted in NSW, Australia comprising all children who were born in NSW born between 2000-2010 with complete follow-up till end of December 31st 2011. Each child was included from birth through the end of the follow up period or in-hospital death, whichever was earlier. The birth cohort was divided in to three sub-groups:

1. Non-Indigenous high-risk children: Non-Indigenous children who 1) were born preterm (gestational age (GA) <37 weeks), 2) were born at term with a birth weight of <2500 grams

2. 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.

3. Non-Indigenous standard risk children: All other non-Indigenous term children.

Variables:

Exposure variables:

The main exposure variable of interest was any episode of RSV coded hospitalization in the cohort child from birth to two years of age, the peak age-group for RSV hospitalizations[13]. The International Classification of Diseases, 10th edition (ICD-10) primary diagnostic codes were used to identify RSV hospitalizations. Any hospitalization with primary diagnostic codes associated with RSV pneumonia (J12.1), acute RSV bronchitis (J20.5), acute RSV bronchiolitis (J21.0), unspecified acute lower respiratory infections (J22), unspecified acute bronchitis (J20.9) and unspecified acute bronchiolitis (J21.9) identified during RSV season (April-September in NSW) were included as RSV hospitalizations.

Outcome variable:

The outcome variable of interest was first episode of asthma hospitalization beyond the age of two years until the end of follow up. All hospitalizations with primary diagnostic codes associated with asthma (J45), predominantly allergic asthma (J45.0), non-allergic asthma (J45.1), mixed asthma (J45.8), asthma unspecified (J45.9) and status asthmaticus (J46) or wheeze (R0.62) were considered as asthma hospitalizations.

Confounders:

Confounders included in the analysis were based on the published literature and included maternal and child factors [14]. Maternal variables were age at birth of the cohort child, parity, smoking during pregnancy and index of socio-economic disadvantage of the mother's residential postcode at birth. Child factors included in the analyses were season of birth and sex of the child.

Data sources:

The Centre for Health Record Linkage (CHeReL) (www.cherel.org.au) in NSW conducts linkage of various administrative health data sets for research purposes. CHeReL follows best practice probabilistic linkage [15] to combine personal information to produce a person-based dataset using the NSW Perinatal data Collection as the primary dataset to which all other datasets are linked. Each child was assigned a Patient Project Number and this was attached to the records in each source database. All other personal identifiers were removed from each of the datasets and the de-identified datasets with the unique identifier key were provided to the study investigators. One of the study investigators (NH) combined records of the same child in the different data sets using the unique identifier key and undertook data cleansing.

The cohort was identified from the NSW Perinatal Data Collection in which all births in NSW are registered. Data relating to any episode of RSV and asthma in the cohort children

were retrieved from the Admitted Patient Data Collection. This data set also contained outcome of each hospitalization including discharge status, death, and need for transfer. The corresponding maternal, perinatal and socio-demographic factors for the cohort children were retrieved from the Perinatal Data Collection which was linked to the Admitted Patient data Collection. Socioeconomic disadvantage based on maternal post code of residence at the time of birth of the cohort child was measured using the SEIFA (Socioeconomic index of areas) Indices of Relative Socioeconomic Advantage and Disadvantage (IRSAD) from the Australian Bureau of Statistics [16].

Bias:

This was a large whole-of-population based cohort study based on almost complete data sets. Out of 1,264,943 observations, there were 7,432 (0.5%) observations with one or more variables missing which were excluded from the final analyses.

Study size:

This was a whole-of-population study including all children born in NSW between 2000-2010 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 <20 years, 20-24 years, 25-29 years, 30-34 years and ≥35 years; 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 and level five was most advantaged and level one was considered as the referent group [16].

Statistical Analyses:

This was a cohort study where children were followed from birth and the risk of subsequent first asthma hospitalization beyond the age of two years was determined using hazard analyses taking age of the child at asthma hospitalization as the relevant time to event.

As the hazard of subsequent asthma hospitalization was non-proportional violating the proportionality hazard assumption of standard Cox model, we used an extended Cox model with time varying covariate to account for the non-proportionality. The age at asthma hospitalization was split in to 2-3 years, 3-5 years, 5-7 years and >7 years age groups and the interaction between baseline RSV risk and subsequent asthma hospitalization was examined for the different age groups. Separate models were constructed for each of the pre-defined sub-group of children. The final multivariable model was adjusted for all available confounders mentioned in the method section. We estimated the hazard ratio (HR) and the 95% Confidence Intervals (CI) around the HR of first asthma hospitalization after the age of two years for children with versus without any RSV hospitalization in their first two years of life.

Ethics approval:

The project was approved by the NSW Population and Health Service Research (HREC/09/CIPHS/33; 2009/05/155) and the Aboriginal Health and Medical Research Council Ethics (726/10).

RESULTS:

Profile of the Cohort:

The cohort comprised 847,516 children born between 2000-2010. Of these, 437,034 (52%) were male and the mean age of the cohort at the end of the follow up period was 73 months (SD±42 months) (Table 1). In total 31,831 (4%) cohort children had at least one episode of RSV hospitalization before the age of two years, of which 2,405 (7.5%) also had an episode of asthma hospitalization after the age of two. The median age at first asthma hospitalization was 3.2 years (IQR 2.5-4.4 years).

Table 1: Perinatal and socio-demographic characteristics of cohort children born in NSW between 2000-2010

N= 847,516		
Exposures	Children with RSV hospitalization in the first two years of life	Children without any RSV hospitalization in the first two years of life
	n=31,831	n=815,685
	n (%)	
Maternal age		
<20 years	2,102 (6)	32,088 (4)
20-24 years	6,342 (19)	113,813 (14)
25-29 years	9,022 (28)	227,139 (28)
30-34 years	9,081 (28)	270,626 (33)
≥35 years	5,284 (17)	172,019 (21)
Maternal smoking during pregnancy	8,178 (26)	112, 584 (14)
Multiparity of the mother	23,211 (73)	470,574 (58)

IRSAD		
1 (most disadvantaged)	4,032 (13)	78,280 (10)
2	4,941 (15)	101,577 (12)
3	8,405 (26)	189,507 (23)
4	7,906 (25)	208,681 (26)
5 (most advantaged)	6,512 (20)	239,566 (29)
Male sex of the baby	18,799 (59)	397,005 (49)
Season of birth		
Summer	8,121 (26)	195,652 (24)
Autumn	10,470 (33)	198,355 (24)
Winter	7,193 (23)	207,579 (25)
Spring	6,047 (19)	214,099 (26)
High-risk children	4,902 (15)	60,637 (7)
Indigenous children	2,960 (9)	26,732 (3)
Non-Indigenous standard risk children	26,172 (82)	741,025 (91)
Asthma hospitalization beyond age of 2 years	2,405 (7.5)	19,974 (2)

Hazard for asthma hospitalization:

In the adjusted multivariable Cox hazard model, the hazard of first asthma hospitalization persisted to be double beyond the age of seven years for children who were hospitalised with RSV in the first two years of life compared to those who were not (Table 2). The adjusted hazard for first asthma hospitalization was highest for children between the ages 2-3 years. The adjusted HR at ages 2-3 years for non-Indigenous standard risk children was 3.9 (95% CI 3.7-4.1), for high-risk children was 4.3 (95% CI 3.8-4.9) and for Indigenous

children was 4.0 (95% CI 3.3-4.8). The risk of asthma hospitalization at different ages was comparable across the different sub-groups of children.

Table 2: Hazard ratio for first asthma hospitalization beyond the age of two years in different sub-groups of children who had severe RSV disease in the first two years of life compared to those who did not: NSW 2000-2010

Age at first asthma hospitalization	Non-Indigenous standard risk children		High-risk children		Indigenous children	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
2-3 years	4.1 (3.9, 4.4)	3.9 (3.7, 4.1)	4.7 (4.2, 5.3)	4.5 (4.0, 5.1)	4.1 (3.4, 4.9)	4.0 (3.3, 4.8)
3-5 years	3.0 (2.9, 3.2)	2.8 (2.7, 3.0)	3.1 (2.7, 3.5)	3.0 (2.7, 3.4)	2.2 (1.8, 2.7)	2.2 (1.8, 2.6)
5-7 years	2.4 (2.2, 2.7)	2.3 (2.1, 2.5)	2.6 (2.1, 3.2)	2.6 (2.1, 3.2)	2.6 (1.9, 3.4)	2.5 (1.9, 3.3)
>7 years	2.8 (2.4, 3.2)	2.6 (2.3, 3.0)	3.5 (2.7, 4.5)	3.4 (2.6, 4.3)	2.0 (1.4, 3.1)	1.9 (1.2, 2.9)

** Hazard ratio after adjusting for mother's age at birth of the cohort child, parity, maternal smoking during pregnancy, index of socio-economic disadvantage of the mother's residential postcode at birth, season of birth and sex of the child.*

DISCUSSION:

To our knowledge this is the first study to demonstrate increased risk of first asthma hospitalization following severe RSV disease in different sub-groups of high-risk children concurrently. Our findings, based on a very large population cohort of children followed up to 11 years of age, suggest that different sub-groups of high-risk children, who developed RSV disease within the first two years of life continue to be at elevated risk of first asthma hospitalization beyond the age of seven years. The hazard of first asthma hospitalization was similar across all sub-groups of children with the hazard being four times higher at ages 2-3 years. Although premature children and Indigenous children aged <2 years are at almost 10 times higher risk of acquiring severe RSV disease compared to standard risk children[13], the similar hazard of subsequent asthma hospitalization across different sub-groups of children suggest that RSV might be the strongest predictor for developing subsequent severe childhood asthma. Thus RSV might not only be the main etiology for acute respiratory illness but also be an important contributor to chronic respiratory morbidity in children suggesting that interventions/therapies to prevent early severe RSV disease will help reduce the burden of subsequent paediatric asthma/wheeze. While there are no effective antivirals or vaccines against RSV disease, at present, there is an effective anti-RSV monoclonal antibody (palivizumab) which can prevent severe RSV disease in high-risk infants including those born preterm and with chronic lung and heart conditions [17 18]. Studies have shown that palivizumab can also prevent subsequent recurrent wheeze in preterm children [19 20] .However use of palivizumab remains limited in Australia and there is no standardised national guideline. Considering the potential beneficial effect of palivizumab on severe RSV diseases and subsequent recurrent wheeze in children, there is a need for revisiting its effectiveness and standardising guidelines with inclusion of Indigenous children as high-risk.

The risk of first asthma hospitalization in our cohort children who had severe RSV disease leading to hospitalization in their first two years of life was significantly higher across all the age strata. It is possible that many of the first asthma hospitalization within ages 2-3 and 3-5 years in our analysis may have been due to recurrent wheeze. Indeed diagnosis of asthma in children aged <5 years is challenging. The Global Initiative for Asthma guideline (GINA) suggest that symptoms including frequent episodes of wheeze, activity-induced cough or wheeze, nocturnal cough without viral infections in periods without viral infections which persist beyond three years of age are suggestive of asthma in children <5years of age [21]. In addition RSV disease has been associated with increased risk of persistent wheezing in children [5 22]. However the risk of first asthma hospitalization in this cohort was also significantly higher at ages 5-7 years and beyond seven years of age. Another longitudinal study done in the UK had also reported that the odds of doctors diagnosed asthma beyond the age of seven was double for children who had RSV hospitalization in the first year of life compared to the those who did not [22]. Other studies have also noted that risk of subsequent asthma following early RSV illness can persist until 11 years of age [5] and even in adulthood [6]. It is believed that early severe lower RSV infection may cause airway remodelling and impair development of the growing lung which persists in later life [23]. Even mild RSV disease may lead to residual impaired lung function in children up to the age of 13 years [5].

An important limitation of the study is that our exposure and outcome variables of interest were coded RSV and asthma hospitalizations; it is possible that some hospitalizations were misclassified because routine laboratory confirmation of RSV may not be a standard clinical practice in some hospitals and the diagnosis of asthma in younger children is a challenge. This was a population based study using administrative data where diagnosis of diseases was based on ICD codes and any possible error with the coding system was beyond

our control. We considered all unspecified episodes of bronchiolitis and bronchitis identified during RSV season which may have led to overestimation or underestimation (as laboratory confirmation of RSV diseases is not necessarily standard clinical practice) of the effect. However, our previous analysis[13] suggests that all cause associated ALRI coded hospitalizations in children aged <2 years during the RSV season follows a similar trend as RSV coded hospitalization which suggests that most paediatric ALRI hospitalizations during the RSV season are likely due to RSV. We did not have access to any information regarding atopic predisposition of children; it is likely that many children hospitalised with asthma were atopic. If early severe RSV disease is also a manifestation of atopic predisposition, it is possible that the observed relationship between RSV and asthma is not causal. However, other studies suggest the association between asthma and RSV is independent of atopic history [24 25]. As this was an epidemiological study causality of the association between RSV and asthma cannot be confirmed, but the findings are comparable to other studies adding to the body of evidence that a strong association exists. We did not have access to ambulatory care data so could not assess the association between less severe forms of RSV infection and asthma not requiring hospitalization. In our cohort there were only 335 hospitalizations coded as associated with any other viral ALRI in the first two years of life, compared with 31,831 RSV-associated ALRI hospitalizations; we therefore did not investigate association between other virus-specific ALRI and asthma. This work compliments the apparent association between RSV disease with the subsequent development of asthma [5], while infections with other viruses like rhino and influenza viruses [26] are more clearly associated with exacerbations of asthma. In addition even if any association exist, their contribution to asthma is likely to be comparatively small.

Our study confirms that hospitalization for severe RSV disease in the first two years of life is associated with the subsequent hospitalization for first episode of asthma

hospitalization in Australian children. While there are currently no effective antivirals or vaccines targeting RSV, several vaccines are being evaluated in clinical trials [27]. Once an effective vaccine becomes available, long term follow-up of children to evaluate the impact on subsequent asthma development will help define the causal pathway of RSV and asthma, particularly in the high-risk groups. Meanwhile, more conservative preventive strategies such as frequent hand washing [28] targeted to prevent transmission RSV diseases may also have the added benefit of reducing the burden of asthma in children.

ACKNOWLEDGEMENTS

The authors would like to thank Sydney Children's Hospital foundation and Rotary Club of Sydney Cove for their continued support in our research endeavours. We are grateful to Respiratory Department of Sydney Children's Hospital, Randwick and Virology Research Laboratory of Prince of Wales Hospital, Randwick for their cooperation. We thank the Aboriginal Health and Medical Research Council and Ministry of Health, NSW. We also thank the babies and their families, the nursing and midwifery, obstetric and medical records staff of the obstetric and children's hospitals in NSW and the ACT.

Authors' contribution: NH and AJ conceived and designed the study. NH, NB and CP was responsible for analysing the data. NH drafted the manuscript. TS, WR, KL, J-L O, LH and BB provided technical feedback with design, analyses and drafting of the manuscript.

Competing interest: None declared

Funding: This work was supported by The Rotary Club of Sydney Cove and the Cerebral Palsy Alliance of Australia. The funding organization had no role in the study design, analyses or drafting of the manuscript.

Data sharing statement: This study used linked administrative data. 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). There is no additional data available.

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STROBE Statement—Checklist of items that should be included in ***cohort studies***

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ASSOCIATION BETWEEN RESPIRATORY SYNCYTIAL VIRAL DISEASE AND THE SUBSEQUENT RISK OF FIRST EPISODE OF SEVERE ASTHMA IN DIFFERENT SUB-GROUPS OF HIGH-RISK AUSTRALIAN CHILDREN: A WHOLE-OF-POPULATION BASED COHORT STUDY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017936.R2
Article Type:	Research
Date Submitted by the Author:	11-Sep-2017
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology, Infectious diseases, Respiratory medicine
Keywords:	Respiratory infections < THORACIC MEDICINE, Asthma < THORACIC MEDICINE, Community child health < PAEDIATRICS

ASSOCIATION BETWEEN RESPIRATORY SYNCYTIAL VIRAL DISEASE AND THE SUBSEQUENT RISK OF FIRST EPISODE OF SEVERE ASTHMA IN DIFFERENT SUB-GROUPS OF HIGH-RISK AUSTRALIAN CHILDREN: A WHOLE-OF-POPULATION BASED COHORT STUDY

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Running title: RSV and risk of first asthma hospitalization

Key words: RSV, asthma, cohort study

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ABSTRACT

Objective: To determine the contribution of respiratory syncytial virus (RSV) to the subsequent development of asthma in different sub-groups of children at risk of severe RSV disease.

Settings: The study was conducted in New South Wales (NSW), Australia

Participants: The study comprised all children born in NSW between 2000-2010 with complete follow-up till December 31st 2011. The cohort was divided in to three sub-groups:

1. Non-Indigenous high-risk children: Non-Indigenous children born preterm or born with a low birth weight.

2. Indigenous children: Children of mothers whose Indigenous status was recorded as Aboriginal and/or Torres Strait Islander.

3. Non-Indigenous standard risk children: All other non-Indigenous term children.

Primary outcome measure: Risk of development of severe asthma in different sub-groups of children who had RSV hospitalisation in the first two years of life compared to those who did not.

Design: We performed a retrospective cohort analysis using population-based linked administrative data. Extended Cox model was used to determine hazard ratio (HR) and 95% confidence interval (CI) around the HR for first asthma hospitalisation in different sub-groups of children.

Results: The cohort comprised 847,516 children born between 2000-2010. In the adjusted Cox model, the hazard of first asthma hospitalisation was higher and comparable across all sub-groups of children who had RSV hospitalisation compared to those who did not. The HR (95% CI) was highest in children aged 2-3 years; 4.3 (95% CI 3.8-4.9) for high-risk, 4.0 (95% CI 3.3-4.8) for Indigenous and 3.9 (95% CI 3.7-4.1) for non-Indigenous standard risk children. This risk persisted beyond seven years of age.

Conclusion: This large study confirms a comparable increased risk of first asthma hospitalisation following RSV disease in the first two years of life across different sub-groups children at risk.

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Strengths and Limitations:

- To our knowledge this is the first study to demonstrate increased risk of first asthma hospitalization following severe RSV disease concurrently in different sub-groups of high-risk children at a population level.
- The study cohort comprised all children born in NSW between 2000-2010 which enabled us to determine the risk of asthma in different age-groups extending beyond seven years.
- This was an epidemiological study using linked administrative data and lacked information relating to factors like atopic predisposition and risk of subsequent asthma in this cohort, hence a causal association cannot be established for RSV hospitalisation.

INTRODUCTION

Background:

Globally, acute lower respiratory infections (ALRIs) are a major cause of childhood morbidity and mortality [1]. Early life respiratory viral infections have been linked to the development of subsequent asthma in children [2]. This link has been particularly highlighted for early respiratory syncytial virus (RSV) infection in children which continues to be the major viral cause of childhood ALRIs in the first two years of life[3]. It has been proposed that severe RSV infection in early childhood is associated with impaired lung function which persists beyond childhood and increases risk of recurrent wheezing and asthma at a later age of life[4 5]. Asthma symptoms associated with severe RSV illness in first year of life can even persist in early adulthood [6]. In addition early RSV hospitalisation may also result in reduced lung function, even in the absence of asthma symptoms [6]. Although there is some evidence that severe RSV disease and allergic sensitisation may be linked via interleukin (IL)-13/IL-4 gene polymorphisms, severe RSV infection in early childhood is possibly a consequence rather than a cause of a predisposition to severe reversible airway diseases [7 8].

Objectives

Australia has a high prevalence of paediatric asthma compared to other developed countries [9 10]. It is estimated that 21% of Australian children aged 0 to 15 years have had a previous diagnosis of asthma, with 11% having a current diagnosis of asthma [11]. In 2014, more than 13,000 children aged 1–17 years presented to New South Wales (NSW) emergency departments for asthma, representing two-thirds of all hospital presentations across the state and yielding a significant burden on the health care system [12]. The burden of RSV-associated lower respiratory tract infection (LRTI) is also very high in NSW, especially in children aged <2 years with an average annual direct health care cost of more than AUD nine million in NSW alone[13]. In addition, our previous study has demonstrated

that the incidence of severe RSV disease was exceptionally high among children who were born preterm or with broncho-pulmonary dysplasia (BPD) and Indigenous children of NSW [13] . It is, therefore, important to determine what, if any, contribution early severe RSV disease has on subsequent asthma hospitalisations in these sub-groups of children at risk. While data exist on the high burden of RSV disease in these sub-groups of children, to our knowledge, no study has investigated the contribution of RSV to subsequent asthma risk in different high-risk paediatric populations simultaneously. Such information will be important to inform targeted public health interventions aimed to lower the burden of severe asthma in Australian children.

To address this knowledge gap, we conducted a retrospective population-based cohort study designed to investigate the role of early RSV ALRI on the subsequent risk of development of severe asthma in different sub-groups of children at risk in NSW.

METHODS:

Study Design:

The study was a retrospective cohort analyses using linked population based administrative data.

Study site & study population:

The study was conducted in NSW, Australia comprising all children who were born in NSW born between 2000-2010 with complete follow-up till end of December 31st 2011. Each child was included from birth through the end of the follow up period or in-hospital death, whichever was earlier. The birth cohort was divided in to three sub-groups:

1. Non-Indigenous high-risk children: Non-Indigenous children who 1) were born preterm (gestational age (GA) <37 weeks), 2) were born at term with a birth weight of <2500 grams

2. 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.

3. Non-Indigenous standard risk children: All other non-Indigenous term children.

Variables:

Exposure variables:

The main exposure variable of interest was any episode of RSV coded hospitalisation in the cohort child from birth to two years of age, the peak age-group for RSV hospitalisations[13]. The International Classification of Diseases, 10th edition (ICD-10) primary diagnostic codes were used to identify RSV hospitalisations. Any hospitalisation with primary diagnostic codes associated with RSV pneumonia (J12.1), acute RSV bronchitis (J20.5), acute RSV bronchiolitis (J21.0), unspecified acute lower respiratory infections (J22),

unspecified acute bronchitis (J20.9) and unspecified acute bronchiolitis (J21.9) identified during RSV season (April-September in NSW) were included as RSV hospitalisations.

Outcome variable:

The outcome variable of interest was first episode of asthma hospitalisation beyond the age of two years until the end of follow up. All hospitalisations with primary diagnostic codes associated with asthma (J45), predominantly allergic asthma (J45.0), non-allergic asthma (J45.1), mixed asthma (J45.8), asthma unspecified (J45.9) and status asthmaticus (J46) or wheeze (R0.62) were considered as asthma hospitalisations.

Confounders:

Confounders included in the analysis were based on the published literature and included maternal and child factors [14]. Maternal variables were age at birth of the cohort child, parity, smoking during pregnancy and index of socio-economic disadvantage of the mother's residential postcode at birth. Child factors included in the analyses were season of birth and sex of the child.

Data sources:

The Centre for Health Record Linkage (CHeReL) (www.cherel.org.au) in NSW conducts linkage of various administrative health data sets for research purposes. CHeReL follows best practice probabilistic linkage [15] to combine personal information to produce a person-based dataset using the NSW Perinatal Data Collection as the primary dataset to which all other datasets are linked. Each child was assigned a Patient Project Number and this was attached to the records in each source database. All other personal identifiers were removed from each of the datasets and the de-identified datasets with the unique identifier key were provided to the study investigators. One of the study investigators (NH) combined records of the same child in the different data sets using the unique identifier key and undertook data cleansing.

The cohort was identified from the NSW Perinatal Data Collection in which all births in NSW are registered. Data relating to any episode of RSV and asthma in the cohort children were retrieved from the Admitted Patient Data Collection. This data set also contained outcome of each hospitalisation including discharge status, death, and need for transfer. The corresponding maternal, perinatal and socio-demographic factors for the cohort children were retrieved from the Perinatal Data Collection which was linked to the Admitted Patient data Collection. Socioeconomic disadvantage based on maternal post code of residence at the time of birth of the cohort child was measured using the SEIFA (Socioeconomic index of areas) Indices of Relative Socioeconomic Advantage and Disadvantage (IRSAD) from the Australian Bureau of Statistics [16].

Bias:

This was a large whole-of-population based cohort study based on almost complete data sets. Out of 1,264,943 observations, there were 7,432 (0.5%) observations with one or more variables missing which were excluded from the final analyses.

Study size:

This was a whole-of-population study including all children born in NSW between 2000-2010 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 <20 years, 20-24 years, 25-29 years, 30-34 years and ≥35 years; 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 and level five was most advantaged and level one was considered as the referent group [16].

Statistical Analyses:

This was a cohort study where children were followed from birth and the risk of subsequent first asthma hospitalisation beyond the age of two years was determined using hazard analyses taking age of the child at asthma hospitalisation as the relevant time to event. As the hazard of subsequent asthma hospitalisation was non-proportional violating the proportionality hazard assumption of standard Cox model, we used an extended Cox model with time varying covariate to account for the non-proportionality. The age at asthma hospitalisation was split in to 2-3 years, 3-5 years, 5-7 years and >7 years age groups and the interaction between baseline RSV risk and subsequent asthma hospitalisation was examined for the different age groups. Separate models were constructed for each of the pre-defined sub-group of children. The final multivariable model was adjusted for all available confounders mentioned in the method section. We estimated the hazard ratio (HR) and the 95% Confidence Intervals (CI) around the HR of first asthma hospitalisation after the age of two years for children with versus without any RSV hospitalisation in their first two years of life.

Ethics approval:

The project was approved by the NSW Population and Health Service Research (HREC/09/CIPHS/33; 2009/05/155) and the Aboriginal Health and Medical Research Council Ethics (726/10).

RESULTS:

Profile of the Cohort:

The cohort comprised 847,516 children born between 2000-2010. Of these, 437,034 (52%) were male and the mean age of the cohort at the end of the follow up period was 73 months (SD±42 months) (Table 1). In total 31,831 (4%) cohort children had at least one episode of RSV hospitalisation before the age of two years, of which 2,405 (7.5%) also had an episode of asthma hospitalisation after the age of two. The median age at first asthma hospitalisation was 3.2 years (IQR 2.5-4.4 years).

Table 1: Perinatal and socio-demographic characteristics of cohort children born in NSW between 2000-2010

N= 847,516		
Exposures	Children with RSV hospitalisation in the first two years of life	Children without any RSV hospitalisation in the first two years of life
	n=31,831	n=815,685
	n (%)	
Maternal age		
<20 years	2,102 (6)	32,088 (4)
20-24 years	6,342 (19)	113,813 (14)
25-29 years	9,022 (28)	227,139 (28)
30-34 years	9,081 (28)	270,626 (33)
≥35 years	5,284 (17)	172,019 (21)
Maternal smoking during pregnancy	8,178 (26)	112, 584 (14)
Multiparity of the mother	23,211 (73)	470,574 (58)

IRSAD		
1 (most disadvantaged)	4,032 (13)	78,280 (10)
2	4,941 (15)	101,577 (12)
3	8,405 (26)	189,507 (23)
4	7,906 (25)	208,681 (26)
5 (most advantaged)	6,512 (20)	239,566 (29)
Male sex of the baby	18,799 (59)	397,005 (49)
Season of birth		
Summer	8,121 (26)	195,652 (24)
Autumn	10,470 (33)	198,355 (24)
Winter	7,193 (23)	207,579 (25)
Spring	6,047 (19)	214,099 (26)
High-risk children	4,902 (15)	60,637 (7)
Indigenous children	2,960 (9)	26,732 (3)
Non-Indigenous standard risk children	26,172 (82)	741,025 (91)
Asthma hospitalisation beyond age of 2 years	2,405 (7.5)	19,974 (2)

Hazard for asthma hospitalisation:

In the adjusted multivariable Cox hazard model, the hazard of first asthma hospitalisation persisted to be double beyond the age of seven years for children who were hospitalized with RSV in the first two years of life compared to those who were not (Table 2). The adjusted hazard for first asthma hospitalisation was highest for children between the ages 2-3 years. The adjusted HR at ages 2-3 years for non-Indigenous standard risk children was 3.9 (95% CI 3.7-4.1), for high-risk children was 4.3 (95% CI 3.8-4.9) and for Indigenous

children was 4.0 (95% CI 3.3-4.8). The risk of asthma hospitalisation at different ages was comparable across the different sub-groups of children.

Table 2: Hazard ratio for first asthma hospitalisation beyond the age of two years in different sub-groups of children who had severe RSV disease in the first two years of life compared to those who did not: NSW 2000-2010

Age at first asthma hospitalisation	Non-Indigenous standard risk children		High-risk children		Indigenous children	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
2-3 years	4.1 (3.9, 4.4)	3.9 (3.7, 4.1)	4.7 (4.2, 5.3)	4.5 (4.0, 5.1)	4.1 (3.4, 4.9)	4.0 (3.3, 4.8)
3-5 years	3.0 (2.9, 3.2)	2.8 (2.7, 3.0)	3.1 (2.7, 3.5)	3.0 (2.7, 3.4)	2.2 (1.8, 2.7)	2.2 (1.8, 2.6)
5-7 years	2.4 (2.2, 2.7)	2.3 (2.1, 2.5)	2.6 (2.1, 3.2)	2.6 (2.1, 3.2)	2.6 (1.9, 3.4)	2.5 (1.9, 3.3)
>7 years	2.8 (2.4, 3.2)	2.6 (2.3, 3.0)	3.5 (2.7, 4.5)	3.4 (2.6, 4.3)	2.0 (1.4, 3.1)	1.9 (1.2, 2.9)

** Hazard ratio after adjusting for mother's age at birth of the cohort child, parity, maternal smoking during pregnancy, index of socio-economic disadvantage of the mother's residential postcode at birth, season of birth and sex of the child.*

DISCUSSION:

To our knowledge this is the first study to demonstrate increased risk of first asthma hospitalisation following severe RSV disease in different sub-groups of high-risk children concurrently. Our findings, based on a very large population cohort of children followed up to 11 years of age, suggest that different sub-groups of high-risk children, who developed RSV disease within the first two years of life continue to be at elevated risk of first asthma hospitalisation beyond the age of seven years. The hazard of first asthma hospitalisation was similar across all sub-groups of children with the hazard being four times higher at ages 2-3 years. Although premature children and Indigenous children aged <2 years are at almost 10 times higher risk of acquiring severe RSV disease compared to standard risk children[13], the similar hazard of subsequent asthma hospitalisation across different sub-groups of children suggest that RSV might be the strongest predictor for developing subsequent severe childhood asthma. Thus RSV might not only be the main etiology for acute respiratory illness but also be an important contributor to chronic respiratory morbidity in children suggesting that interventions/therapies to prevent early severe RSV disease will help reduce the burden of subsequent paediatric asthma/wheeze. While there are no effective antivirals or vaccines against RSV disease, at present, there is an effective anti-RSV monoclonal antibody (palivizumab) which can prevent severe RSV disease in high-risk infants including those born preterm and with chronic lung and heart conditions [17 18]. Studies have shown that palivizumab can also prevent subsequent recurrent wheeze in preterm children [19 20] .However use of palivizumab remains limited in Australia and there is no standardised national guideline. Considering the potential beneficial effect of palivizumab on severe RSV diseases and subsequent recurrent wheeze in children, there is a need for revisiting its effectiveness and standardising guidelines with inclusion of Indigenous children as high-risk.

The risk of first asthma hospitalisation in our cohort children who had severe RSV disease leading to hospitalisation in their first two years of life was significantly higher across all the age strata. It is possible that many of the first asthma hospitalisation within ages 2-3 and 3-5 years in our analysis may have been due to recurrent wheeze. Indeed diagnosis of asthma in children aged <5 years is challenging. The Global Initiative for Asthma guideline (GINA) suggest that symptoms including frequent episodes of wheeze, activity-induced cough or wheeze, nocturnal cough without viral infections in periods without viral infections which persist beyond three years of age are suggestive of asthma in children <5years of age [21]. In addition RSV disease has been associated with increased risk of persistent wheezing in children [5 22]. However the risk of first asthma hospitalisation in this cohort was also significantly higher at ages 5-7 years and beyond seven years of age. Another longitudinal study done in the UK had also reported that the odds of doctors diagnosed asthma beyond the age of seven was double for children who had RSV hospitalisation in the first year of life compared to the those who did not [22]. Other studies have also noted that risk of subsequent asthma following early RSV illness can persist until 11 years of age [5] and even in adulthood [6]. It is believed that early severe lower RSV infection may cause airway remodelling and impair development of the growing lung which persists in later life [23]. Even mild RSV disease may lead to residual impaired lung function in children up to the age of 13 years [5].

An important limitation of the study is that our exposure and outcome variables of interest were coded RSV and asthma hospitalisations; it is possible that some hospitalisations were misclassified because routine laboratory confirmation of RSV may not be a standard clinical practice in some hospitals and the diagnosis of asthma in younger children is a challenge. This was a population based study using administrative data where diagnosis of diseases was based on ICD codes and any possible error with the coding system was beyond

our control. We considered all unspecified episodes of bronchiolitis and bronchitis identified during RSV season which may have led to overestimation or underestimation (as laboratory confirmation of RSV diseases is not necessarily a standard clinical practice) of the effect. However, our previous analysis[13] suggests that all cause associated ALRI coded hospitalisations in children aged <2 years during the RSV season follows a similar trend as RSV coded hospitalisation and RSV notification data which suggests that most paediatric ALRI hospitalisations during the RSV season are likely due to RSV. We did not have access to any information regarding atopic predisposition of children; it is likely that many children hospitalised with asthma were atopic. If early severe RSV disease is also a manifestation of atopic predisposition, it is possible that the observed relationship between RSV and asthma is not causal. However, other studies suggest the association between asthma and RSV is independent of atopic history [24 25]. As this was an epidemiological study causality of the association between RSV and asthma cannot be confirmed, but the findings are comparable to other studies adding to the body of evidence that a strong association exists. We did not have access to ambulatory care data so could not assess the association between less severe forms of RSV infection and asthma not requiring hospitalisation. In our cohort there were only 335 hospitalisations coded as associated with any other viral ALRI in the first two years of life, compared with 31,831 RSV-associated ALRI hospitalisations; we therefore did not investigate association between other virus-specific ALRI and asthma. This work compliments the apparent association between RSV disease with the subsequent development of asthma [5], while infections with other viruses like rhino and influenza viruses [26] are more clearly associated with exacerbations of asthma. In addition even if any association exist, their contribution to asthma is likely to be comparatively small.

Our study confirms that hospitalisation for severe RSV disease in the first two years of life is associated with the subsequent hospitalisation for first episode of asthma

hospitalisation in Australian children. While there are currently no effective antivirals or vaccines targeting RSV, several vaccines are being evaluated in clinical trials [27]. Once an effective vaccine becomes available, long term follow-up of children to evaluate the impact on subsequent asthma development will help define the causal pathway of RSV and asthma, particularly in the high-risk groups. Meanwhile, more conservative preventive strategies such as frequent hand washing [28] targeted to prevent transmission of RSV disease may also have the added benefit of reducing the burden of asthma in children.

ACKNOWLEDGEMENTS

The authors would like to thank Sydney Children's Hospital foundation and Rotary Club of Sydney Cove for their continued support in our research endeavours. We are grateful to Respiratory Department of Sydney Children's Hospital, Randwick and Virology Research Laboratory of Prince of Wales Hospital, Randwick for their cooperation. We thank the Aboriginal Health and Medical Research Council and Ministry of Health, NSW. We also thank the babies and their families, the nursing and midwifery, obstetric and medical records staff of the obstetric and children's hospitals in NSW and the ACT.

Authors' contribution: NH and AJ conceived and designed the study. NH, NB and CP was responsible for analysing the data. NH drafted the manuscript. TS, WR, KL, J-L O, LH and BB provided technical feedback with design, analyses and drafting of the manuscript.

Competing interest: None declared

Funding: This work was supported by The Rotary Club of Sydney Cove and the Cerebral Palsy Alliance of Australia. The funding organization had no role in the study design, analyses or drafting of the manuscript.

Data sharing statement: This study used linked administrative data. 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). There is no additional data available.

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STROBE Statement—Checklist of items that should be included in ***cohort studies***

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