Association of Age at First Severe Respiratory Syncytial Virus Disease With Subsequent Risk of Severe Asthma: A Population-Based Cohort Study

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Objective. In a population-based cohort study, we determined the association between the age at first severe respiratory syncytial virus (RSV) disease and subsequent asthma.

Methods. Incidence rates and rate ratios of the first asthma-associated hospitalization after 2 years of age in children hospitalized for RSV disease at <3 months, 3 to <6 months, 6 to <12 months, and 12–24 months of age were calculated.

Results. The incidence of asthma-associated hospitalization per 1000 child-years among children hospitalized for RSV disease at <3 months of age was 0.5 (95% confidence interval [CI], 0.2–0.7); at 3 to <6 months of age, 0.9 (95% CI, 0.5–1.3); at 6 to <12 months of age, 2.0 (95% CI, 1.4–2.7); and at 12–24 months of age, 1.7 (95% CI, 1.0–2.5). The rate ratio of hospitalization for asthma was 2–7-fold greater among children hospitalized for RSV disease at ages ≥6 months than that among those hospitalized for RSV disease at ages 0 to <6 months.

Conclusions. Although the burden of RSV disease is highest in children aged <6 months, the burden of subsequent asthma is higher in children who develop RSV disease at ages ≥6 months.

Keywords. Age at first RSV; asthma; RSV vaccine.

Globally, acute lower respiratory tract infection (ALRI) associated with respiratory syncytial virus (RSV) infection in the first 2 years of life is the most important cause of childhood acute respiratory morbidity and hospitalization [1]. In 2015, it was estimated that RSV was associated with 3 million hospitalizations in children aged <5 years around the world [2]. The annual rate of hospitalization for RSV disease ranges between 1 and 6 events per 1000 children aged <5 years in industrialized countries [3–6]. The disease rate is highest among children aged 6 weeks to 6 months [6, 7].

There is now a burgeoning body of evidence suggesting that severe RSV disease in the first year of life is a significant risk factor for subsequent asthma and recurrent wheeze in children [8–10]. Our previous population-based study has shown that children who develop severe RSV disease in the first 2 years of life have at least a 2–4-fold higher risk of subsequent acute asthma than children who do not [11]. Asthma is the most common chronic reactive airway disease of childhood and is associated with frequent emergency department and unscheduled physician visits, resulting in a significant healthcare burden [12]. Frequent presentations to the hospital for asthma also result in school absenteeism and academic underperformance [13–15], substantially burden the health system and families, and contribute to psychological stress [16]. Several published studies have demonstrated that children who develop severe RSV disease in early childhood have a 2–4-fold increased risk of subsequent hospitalization for asthma, compared with children who do not, and this risk of hospitalization for asthma persists beyond the first decade of life [8–10].

Owing to the substantial burden of acute and chronic childhood respiratory diseases associated with RSV, development of an effective RSV vaccine is a global public health priority. There are at least 10 different RSV vaccines in different phases of clinical trials [17, 18]. The most advanced candidate vaccine is a maternal RSV vaccine, which is being tested in a phase 3 clinical trial. The goal of this vaccine is to protect infants in their first 6 months of life, when the burden of severe RSV disease is highest, through passive transfer of maternal antibody by a single dose of vaccine administered to pregnant women during the third trimester of pregnancy [17, 18]. A successful RSV vaccination strategy should not only help reduce the burden of acute respiratory illness associated with RSV but also have a protective effect against later
chronic airway disease associated with early RSV infection. However, it is unknown whether protecting children against severe RSV disease in the first 6 months of life through vaccination will also protect them from the subsequent risk of RSV-associated asthma. Therefore, it is important to determine the association between the age when children first develop severe RSV disease and their subsequent risk of asthma. An assessment of a potential association between the age at first hospitalization for RSV disease and the subsequent risk of asthma could inform future maternal and infant RSV vaccination strategies. To address this knowledge gap, we conducted a retrospective, population-based cohort study to investigate whether there was any association between the age at first severe RSV disease and the subsequent risk of asthma in children who develop their first episode of severe RSV disease in the first 2 years of life.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort analysis using linked population-based administrative data.

Study Site and Population

The study was conducted in New South Wales (NSW), Australia, and comprised all children who were born in NSW during 2001–2010 with follow-up ending on 31 December 2011 and who had an RSV-coded hospitalization before age 2 years. The study population was an open cohort. Each child was followed from the first hospitalization for RSV disease (only children who were first hospitalized with RSV disease in the first 2 years of life were included in the cohort) until the child was first hospitalized for asthma or until the end of the study period (31 December 2011), whichever was earlier.

Data Sources

In NSW, the Centre for Health Record Linkage (CHeReL; available at: http://www.cherel.org.au) conducts linkage of various administrative health data sets for research purposes [19]. The CHeReL follows best practices for probabilistic linkage to combine personal information to produce a person-based data set, using the NSW Perinatal Data Collection (PDC) as the primary data set to which all other data sets are linked. Each child was assigned a patient project number, which was attached to the records in each source database including the Admitted Patient Data Collection (APDC). All other personal identifiers were removed from each of the data sets, and the deidentified data sets with the unique identifier key were provided to the study investigators. One of the study investigators (N. H.) combined records of the same child in the PDC and the APDC, using the patient project number.

Variables

Exposure Variable

The main exposure variable of interest was the age of the child at the time of the first RSV-coded hospitalization between birth and 2 years of age, which was retrieved from the APDC system. The age at first hospitalization for RSV disease was stratified as <3 months, 3 to <6 months, 6 to <12 months, and 12–24 months, in line with nominal categories frequently used in analyses of childhood infectious diseases. International Classification of Diseases, Tenth Edition (ICD-10), diagnostic codes were used to identify hospitalizations for RSV disease. Any hospitalizations with RSV-specific codes, including RSV pneumonia (J12.1), acute RSV bronchitis (J20.5), acute RSV bronchiolitis (J21.0), and RSV organism (B97.4), in either the principal or other diagnosis fields were considered as hospitalizations for RSV disease.

Outcome Variable

Because we were primarily interested in the association between age at first severe RSV disease and age at first severe asthma episode, the outcome variable was age at first episode of asthma-coded hospitalization. Because asthma diagnosis is difficult before age 2 years [20], only the first hospitalization for asthma beyond age 2 years was included in the analysis. Age at first hospitalization for asthma was stratified as 2–3 years, 4–5 years, 6–7 years, and >7 years. All hospitalizations with asthma-specific codes, including asthma (J45), predominantly allergic asthma (J45.0), nonallergic asthma (J45.1), mixed asthma (J45.8), asthma unspecified (J45.9), and status asthmaticus (J46), were considered hospitalizations for asthma. Data on hospitalizations for asthma were retrieved from the APDC.

Other Covariates

Data on maternal and child factors that have been previously shown to be associated with an increased risk of RSV disease [21], including multiparity of the mother (a previous pregnancy lasting >20 weeks or first birth was used as a surrogate measure for having elder siblings at home), mode of delivery, maternal smoking during pregnancy, Indigenous status of the mother, residential postcode of the mother at birth, small for gestational age, and sex of the cohort child were ascertained from the PDC. We also collected data from the APDC system on the history of other viral respiratory hospitalizations in the first 2 years of life associated with ICD codes for influenza virus, rhinovirus, parainfluenza virus, and human metapneumovirus. The socioeconomic index of areas and the index of relative socio-economic advantage and disadvantage (IRSAD), compiled by the Australian Bureau of Statistics, were used to construct socioeconomic disadvantage from the postcode of maternal residence at the time of delivery, recorded in the PDC [22].

Statistical Analysis

Poisson regression with robust standard error clustered by individual was used to estimate the incidence rate and rate ratios of subsequent hospitalization for asthma in children who were first hospitalized for RSV disease in the first 2 years of life. The median length of stay during the first hospitalization for asthma was estimated for children in each of age group evaluated for
hospitalization for RSV disease (ie, <3 months, 3 to <6 months, 6 to <12 months, and 12–24 months). We also calculated the incidence of first hospitalization for asthma at ages 2–3 years, 4–5 years, 6–7 years, and >7 years among children in each age group evaluated for hospitalization for RSV disease. The incidence rates and rate ratios were adjusted for parity of the mother, maternal smoking during pregnancy, Indigenous status, IRSAD, sex of the child, and hospitalization associated with other respiratory viruses in the first 2 years of life. A total of 0.5% of variables had missing data, including Indigenous status of the mother, socioeconomic disadvantage in the area of residence, and maternal smoking during pregnancy. Observations with ≥1 missing variable were dropped from the analyses. Analyses were conducted using Stata/SE, version 14.2.

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
There were 888 154 children who were born during and resided in NSW during 2001–2010. A total of 18 042 children (2.0%) had ≥1 hospitalization for RSV disease within the first 2 years of life and were included in our analyses; 1036 children were followed for >7 years. Of the 18 042 children, 57% (10 268) were hospitalized for RSV disease within the first 6 months of life (Table 1), of whom 1374 (7.6%) were also subsequently first hospitalized for asthma beyond age 2 years (309 of 6158 who were first hospitalized for RSV disease at ages <3 months; 286 of 4110, at ages 3 to <6 months; 412 of 4540, at ages 6 to <12 months; and 367 of 3234, at ages 12–24 months). In our cohort, 1775 children (9.8%) had ≥2 hospitalizations for RSV disease in the first 2 years of life, of whom 195 (11.0%) were subsequently hospitalized with their first episode of asthma beyond age 2 years, compared with 1179 of 16 267 (7.2%) who had 1 hospitalization for RSV disease.

Association Between Age at First Hospitalization for RSV Disease and Age at First Hospitalization for Asthma
The adjusted incidence of first hospitalization for asthma beyond age 2 years among children hospitalized for RSV disease in the first 2 years of life was 1.1 events/1000 child-years (95% CI, .9–1.3) overall, 1.2 events/1000 child-years (95% CI, .8–1.4) for boys, and 1.0 events/1000 child-years (95% CI, .7–1.3) for girls. The adjusted incidence of first hospitalization for asthma beyond age 2 years among children who were hospitalized for RSV disease during the first 2 years of life ranged from 0.2 to 2.7 events/1000 child-years among the 4 evaluated age groups (Table 2).

The adjusted incidence of first hospitalization for asthma beyond age 2 years among children who were first hospitalized for RSV disease at age <3 months was 0.5 events/1000 child-years (95% CI, .2–.7; the full adjusted model is presented in Supplement 1). The incidence rate ratios of first hospitalization for asthma beyond age 2 years was 1.9 (95% CI, .1–3.7) among children who were first hospitalized for RSV disease at ages 3 to <6 months, 4.4 (95% CI, 2.5–7.8), for those first hospitalized for RSV disease at ages 6 to <12 months, and 3.8 (95% CI, 2.0–7.2) for those first hospitalized for RSV disease at ages 12–24 months, compared with those first hospitalized for RSV disease at ages <3 months. The median duration of the first hospitalization for asthma was 1.6 days across the different age groups at first hospitalization for RSV disease (Supplement 2).

Children who were hospitalized for RSV disease in the first 2 years of life had the highest rate of subsequent hospitalization for the first episode of asthma at ages 2–3 years, at 39.7

| Table 1. Sociodemographic Profile of 18 042 Children With ≥1 Episode of Severe Respiratory Syncytial Virus (RSV) Disease in the First 2 Years of Life |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Factor          | <3 mo (n = 6158)| 3 to <6 mo (n = 4110)| 6 to <12 mo (n = 4540)| 12–24 mo (n = 3234)|
| Percentage of cohort | 34 | 23 | 25 | 18 |
| Male sex        | 3405 (55) | 2418 (59) | 2719 (60) | 1734 (54) |
| Maternal smoking during pregnancy | 1285 (21) | 1145 (28) | 1106 (24) | 599 (18.5) |
| Born to Indigenous mother | 360 (6) | 291 (7) | 253 (6) | 129 (4) |
| Multiparity of mother | 4904 (78) | 3070 (75) | 3257 (72) | 2001 (62) |
| Vaginal delivery | 3909 (63) | 2590 (63) | 2677 (59) | 1831 (57) |
| IRSADa          | 1 | 2 | 3 | 4 | 5 |
| 1               | 758 (12) | 591 (14) | 571 (13) | 381 (12) |
| 2               | 872 (14) | 612 (15) | 632 (14) | 414 (13) |
| 3               | 1512 (24.5) | 1001 (24) | 1071 (24) | 719 (22) |
| 4               | 1551 (25) | 1071 (26) | 1126 (25) | 802 (25) |
| 5               | 1484 (24) | 835 (20) | 1140 (25) | 917 (28) |

Data are no. (%) of children, unless otherwise indicated.

aThe index of relative socioeconomic advantage and disadvantage (IRSAD) defines “1” as most disadvantaged and “5” as most advantaged.
events/1000 child-years (95% CI, 29.1–50.4). The incidence was 27.4 events/1000 child-years (95% CI, 18.8–36.0) at ages 4–5 years, 11.6 events/1000 child-years (95% CI, 3.5–19.8) at ages 6–7 years, and 23.4 events/1000 child-years (95% CI, 8.8–38.1) at >7 years of age. The unadjusted rates are presented in Supplement 3. The incidence rates of first hospitalization for asthma beyond 2 years of age were not significantly higher in children who had multiple hospitalizations for RSV disease in the first 2 years of life, compared with those who had only 1 hospitalization for RSV disease (incidence rate ratio, 0.9; 95% CI, 0.5–1.6; \( P = .8 \); Table 3).

Children who were first hospitalized for RSV disease at ages 6 to <12 months had the highest rates of subsequent hospitalization for asthma, with values of 46.7 events/1000 child-years (95% CI, 24.2–69.2) at ages 2–3 years, 39.1 events/1000 child-years (95% CI, 23.5–54.6) at ages 4–5 years, 17.4 events/1000 child-years (95% CI, 4.7–30.2) at ages 6–7 years, and 37.9 events/1000 child-years (95% CI, 13.0–62.8) at ages >7 years (Figure 1).

**DISCUSSION**

This large, population-based study is the first to demonstrate that the rate of subsequent hospitalization for asthma was at least 2–7-fold greater in children who had their first episode of severe RSV disease after the first 6 months of life, compared with children who were hospitalized for RSV disease in the first 6 months of life. In our cohort, by 7 years of age, 10% of children who were first hospitalized for RSV disease at ages ≥6 months also had their first hospitalization for asthma, compared with up to 6% children who were first hospitalized for RSV disease in the first 6 months of life. A previous study by Wu et al [23] noted that severe bronchiolitis at any age during infancy was associated with an increased risk of developing childhood asthma, which contradicts our findings. However, the authors investigated the association between all cases of severe bronchiolitis in infancy and their association with subsequent asthma, and our study investigated the association between age at first RSV-specific severe respiratory illness and subsequent asthma. Studies suggest that rhinovirus-associated respiratory illness in infancy is also associated with subsequent asthma, which makes comparability of our results difficult [24]. Additionally, several studies have investigated the association between hospitalized and nonhospitalized cases of RSV disease and demonstrated an increased risk of asthma among individuals hospitalized for RSV disease [8, 9], none of the published studies have actually investigated whether this risk of subsequent asthma varied with the age at which the child first developed severe RSV disease. These studies have also not investigated the association between severe RSV disease beyond infancy and subsequent asthma. The lack of published data makes comparability of our results difficult. Nevertheless, our findings are timely and have important implications for vaccine development and prioritization. Children in 2 distinct priority age groups are being targeted for RSV vaccines. The primary group being targeted for RSV vaccination is children aged <6 months, among whom the burden of RSV disease is highest, through maternal vaccination [17, 18]. The second priority age group includes children aged 6–24 months, with the aim to protect children in the first 2 years of life and to prevent secondary household transmission through active immunization [25]. Unfortunately, in recent years, children in the latter age group have gained less attention from the vaccine developers [25]. Although an effective maternal vaccine will play a pivotal role in substantially lowering the burden of RSV-associated lower respiratory tract infections in children aged <6 months, our data suggest that an effective vaccine for children aged ≥6 months will have a beneficial impact on the long-term consequences of RSV disease, as well.

The development of asthma following early RSV infection is likely due to short-term and long-term alterations in the airway physiology and in the airway immune response [26]. The extent of airway damage is probably linked to the severity of the first episode of RSV disease [27]. Younger infants aged <6 months are probably at highest risk of severe RSV disease, owing to incomplete lung and immune system maturation [26]. However

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**Table 2. Adjusted Incidence of First Hospitalization for Asthma After 2 Years of Age, by Age at First Hospitalization for Respiratory Syncytial Virus Disease in the First 2 Years of Life**

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence, Events/1000 Child-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 2–3 y</td>
<td></td>
</tr>
<tr>
<td>Ages 4–5 y</td>
<td></td>
</tr>
<tr>
<td>Ages 6–7 y</td>
<td></td>
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<tr>
<td>Ages &gt;7 y</td>
<td></td>
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<tr>
<td>&lt;3 mo</td>
<td>0.5 (2.7)</td>
</tr>
<tr>
<td>3 to &lt;6 mo</td>
<td>0.9 (1.3)</td>
</tr>
<tr>
<td>6 to &lt;12 mo</td>
<td>2.0 (1.4–2.7)</td>
</tr>
<tr>
<td>12–24 mo</td>
<td>1.7 (1.0–2.5)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

**Table 3. Age-Specific Adjusted Incidence of Hospitalization for Asthma, by Number of Hospitalizations for Respiratory Syncytial Virus Disease in the First 2 Years of Life**

<table>
<thead>
<tr>
<th>Hospitalizations</th>
<th>Incidence, Events/1000 Child-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 2–3 y</td>
<td></td>
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<tr>
<td>Ages 4–5 y</td>
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<tr>
<td>Ages 6–7 y</td>
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<tr>
<td>Ages &gt;7 y</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41.1 (29.3–52.9)</td>
</tr>
<tr>
<td>≥2</td>
<td>6.9 (76.46.2)</td>
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<tr>
<td>≥2</td>
<td>23.5 (170–54.1)</td>
</tr>
<tr>
<td>≥2</td>
<td>0.000 (NA)</td>
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</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable.
maternal antibody against RSV has a half-life of 76–81 days [28] and provides protection against severe disease during the first RSV season [29]. It may be possible that, even though children are frequently hospitalized with RSV in the first 6 months of life, the severity of disease at the time of hospitalization and the extent of airway damage are linked to the level of maternal antibody in the infants. Indeed, in our cohort, we see a dose-response relationship between increased rates of subsequent hospitalization for asthma and increasing age at first episode of severe RSV disease, which may be due to the waning level of maternal antibody. The first 6 months of life is also the time for rapid lung alveolar multiplication and airway remodeling. Thus, it could be that alteration to the lower airway due to severe RSV disease in the first 6 months of life is transient and improves as the pathogen clears. On the other hand, lung alveolarization is completed by ages 2–3 years [30, 31], and therefore it is possible that severe RSV disease beyond infancy is associated with disruption of the alveolarization process, leading to a persistent adverse impact on lung development and function. Another explanation could be that children whose first episode of RSV disease severe enough to require hospitalization occurs after 6 months of life as opposed to the approximately 60% of infants who develop severe RSV disease in the first 6 months of life, already have some underlying abnormalities that increase their susceptibility of subsequently developing asthma. Additionally, we have also shown that multiple hospitalizations for RSV disease in the first 2 years of life were not associated with an increased risk of subsequent asthma, compared with a single hospitalization for RSV disease. It is possible that the type of host immune response that is activated on reinfection with RSV determines the subsequent risk of asthma [32]. However, because of a lack of published data on the association between age-specific first severe RSV disease and subsequent asthma, these assumptions cannot be confirmed. Additionally, this was an observational study and could not determine the underlying mechanism of the observed relationship. Hence, there is need for further longitudinal studies investigating the natural pathogenesis of disease.

One of the major limitations of our study is that we had to rely on coded hospitalization data to identify hospitalizations for RSV and asthma. This was a population-based study using administrative data, and ICD codes were the only option to ascertain exposure and outcome status. Any error with the coding system was beyond our control. However, such errors are likely to have been nondifferential and would most likely have led to conservative estimates of associations. In NSW, it is not possible to link hospitalization data with laboratory data; hence, it was not possible for us to ascertain whether the RSV-coded hospitalizations were due to laboratory-confirmed RSV infection. However, it is highly likely that an episode of RSV-coded hospitalization was confirmed by laboratory diagnosis. Additionally, our previous study showed that RSV-coded hospitalizations and laboratory-confirmed RSV infections followed a similar distribution [6]. Furthermore, it is likely that many of the asthma-coded hospitalizations in the first 2–3 years of life were actually due to viral wheeze, as diagnosis of asthma is challenging in the first 3 years of life [33]. However, our study was conducted longitudinally over 11 years and demonstrated increased rates of hospitalization for asthma beyond 7 years of life. Additionally, we excluded all hospitalizations coded as wheeze (R0.62) from our analysis. We did not have access to ambulatory care data, so we could not assess the association between age at first RSV infection and occurrence of asthma not requiring hospitalization. Additionally, because our cohort children were aged <2 years at the beginning of the study period,
we did not have data on their lung function at the beginning of follow-up, which could have strengthened the observed association. Because the study population was an open cohort, there were fewer children followed beyond 7 years of age, which may have resulted in wider 95% CIs around our estimates in that age group. Last, this was an epidemiological study, and a causal inference cannot be confirmed. Further studies in different settings will help establish a causal relationship.

Our study has demonstrated that age at first episode of severe RSV disease is linked with the subsequent risk of asthma. The rate of subsequent asthma is higher in children who develop severe RSV disease after the first 6 months of life, compared with those who develop severe RSV disease within the first 6 months of life, and this increased rate of hospitalization for asthma continue to be higher beyond 7 years of age. When effective RSV vaccines become available, passive immunization through maternal vaccination, followed by active immunization in the first 2 years of life, may help in lowering the burden of acute and chronic childhood respiratory diseases associated with RSV.

Supplementary Data
Supplementary materials are available at The Journal of Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
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