Hospitalization for Respiratory Syncytial Virus Infection and Invasive Pneumococcal Disease in Danish Children Aged <2 Years: A Population-Based Cohort Study

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Background. Previous population-based studies have reported a temporal association between respiratory syncytial virus (RSV) infection and invasive pneumococcal disease (IPD). We examined this association at an individual level in the Danish population.

Methods. Using registry information about hospitalization for RSV infection and IPD in Denmark, we conducted a prospective, population-based cohort study and examined the associations between hospitalization for RSV infection and IPD.

Results. In our cohort, no persons aged ≥2 years experienced IPD within 30 days after hospitalization for RSV infection. Among children aged <2 years, children who were hospitalized for RSV infection had a significantly increased risk of IPD during the 30 days after hospitalization, compared with those who were not hospitalized for RSV infection (adjusted rate ratio, 7.1; 95% confidence interval, 3.6–14.3). Likewise, hospitalization for a non-RSV respiratory infection increased the risk of IPD during the 30 days after hospitalization (adjusted rate ratio, 4.5; 95% confidence interval, 2.0–10.0). IPD did not increase the risk of hospitalization for RSV infection among children aged <2 years.

Conclusions. Both recent hospitalization for RSV infection and recent hospitalization for non-RSV respiratory infection increased the risk of IPD among Danish children aged <2 years.

Epidemiological and biological evidence indicates that respiratory viruses contribute to bacterial infections [1–5]. In a recent vaccine trial involving a low-income population, vaccination with a 9-valent pneumococcal conjugate vaccine prevented 30%–60% of cases of viral pneumonia among hospitalized children [6, 7], suggesting that the severity of viral airway infections might depend on increased invasiveness of colonizing bacteria during the acute viral infection.

Previous studies have shown a clear temporal association between severe respiratory syncytial virus (RSV) infection and invasive pneumococcal disease (IPD) at a population level [8–10]. However, the association has not been examined at an individual level. Moreover, earlier studies examined the risk of bacterial infection after viral infection; however, the risk of viral infection after bacterial infection has not been examined.

In high-income populations, the incidence rate of hospitalization for RSV infection among children aged <2 years is ~1000 cases per 100,000 population, and the incidence rate of IPD among the same age group is 45 cases per 100,000 population. Thus, the probability of RSV infection and IPD occurring in the same individual at the same time is low; this finding is also supported by the fact that concurrent serious bacterial infection in infants and children hospitalized with RSV infection is rare [11–13].

It is not clear to what extent viral airway infection
might lead to IPD or whether the association could be explained by common determinants of both conditions. Such determinants could be either genetic or environmental in origin. Recognized common risk factors during childhood are prematurity, low birth weight, comorbidities, crowding with siblings or day care attendance, tobacco smoke exposure, and socioeconomic status—all factors known to increase the risk of hospitalization for RSV infection [14, 15] and IPD [16, 17]. Shared risk factors on a population level during the winter season in temperate climates could be crowding and seasonal immunologic changes [18, 19].

In the present study, we examined the association between hospitalization for RSV infection or non-RSV respiratory infection and IPD, on both a population and an individual level, by testing the hypothesis that hospitalization with RSV infection increases the risk of IPD and that IPD increases the risk of hospitalization for RSV infection. Using national population-based registries, we identified cases of hospitalization for RSV infection and IPD in the Danish population and examined both the temporal association between the diseases and the associations (adjusted for patients age and sex and calendar period) between individual cases of RSV infection and IPD.

METHODS

Using information from 4 Danish population-based registries, we performed a prospective analysis of a longitudinal cohort. The cohort consisted of the entire Danish population from 1 January 1996 to 1 July 2003 and was constructed by register linkage using a unique personal identification number.

**The Danish Civil Registration System.** The study cohort was based on the Danish Civil Registration System, a registry that keeps daily updated demographic information on all residents in Denmark [20]. In the Danish Civil Registration System, each Danish person has a unique identification number, the central person registry number, which serves as a key reference to the individual in all public registries in Denmark.

**The Danish Pneumococcus Database.** IPD was defined as isolation of *Streptococcus pneumoniae* from a normally sterile body site. Patients, identified by the central person registry number, were selected from the Danish Pneumococcus Database, a database established in 1938 as part of a national surveillance program of IPD among hospitalized patients in Denmark. All first-event IPD cases diagnosed from 1 January 1996 through 1 July 2003 were included in the study.

**The RSV database.** The RSV database included the central person registry number, date, and result of the RSV test for Danish hospitalized patients tested for RSV from 1 January 1996 through 1 July 2003. We validated the RSV database against the Danish National Patient Registry, which contains details of all hospitalizations in Denmark, and found that 96% of all positive results of RSV tests performed in Denmark during the study period were registered in the RSV database [21]. The assays routinely used for RSV detection during the study period were based on ELISA or immunofluorescence techniques, which are known to have a lower sensitivity than the newer PCR-based tests [22].

The RSV database defined 2 groups of hospitalized children tested for RSV: the RSV-positive children and the RSV-negative children (i.e., children who were hospitalized for non-RSV respiratory infections). The RSV-negative children were sufficiently ill to be hospitalized and tested for RSV, but the pathogen that caused the disease was unknown. Eighty-three percent of the RSV-negative children had received a diagnosis of respiratory illness for that particular hospitalization in the Danish National Patient Registry (L.G.S., unpublished data) [20].

**The Danish National Patient Registry.** Information about chronic disease was extracted from the Danish National Patient Registry, a registry that contains information on hospital admissions, treatment, and discharge diagnoses for all patients treated in Danish hospitals since 1977 [23]. Outpatient and emergency department hospital contacts have also been recorded in this registry since 1995. Chronic disease in the study population was defined as the occurrence of the following conditions from the start of follow-up until 14 days before the IPD and RSV event: cancer (all except benign), chronic cardiovascular disease, chronic lung disease (including cystic fibrosis), chronic renal disease, gastrointestinal disease, functional and anatomic asplenia, chronic endocrine disorders, neurological disease (all except infectious), autoimmune disease, hematological disease, congenital immunodeficiencies, and birth defects. The date of the first diagnosis of a condition within the selected diagnostic codes was considered to be the date of onset of the chronic disease. The total number of hospital contacts was defined as the sum of every hospital contact registered at a Danish hospital from the start of follow-up until 14 days before an IPD and RSV event. Hospital contacts had to be separated by 1 day to be considered as new contacts. The total duration of hospitalization was defined as the sum of days spent in the hospital from the start of follow-up until 14 days before an IPD and RSV event. A 14-day lag period was defined for each of the variables (chronic disease, number of hospital contacts, and duration of hospitalization), because RSV infection and IPD were reasons for hospital admission.

**Statistical analysis.** The association between RSV infection and IPD was expressed as rate ratios (RRs) estimated by Poisson regression using the SAS GENMOD procedure (SAS). Thus, the rate of IPD among children hospitalized with RSV infection was compared with the rate of IPD observed among the background population of children who were not hospitalized for RSV infection, and the rate of hospitalizations for RSV infection among children with IPD was compared with the rate of hospitalizations among children who did not have IPD. Persons...
in the cohort contributed person-time to follow-up from birth or 1 January 1996 (whichever occurred last) until the date of outcome, death, emigration, or 1 July 2003 (whichever occurred first). Persons with identical dates of RSV infection and IPD diagnoses were excluded. Because the temporal correlation pattern between RSV infection and IPD was different among young children, compared with older individuals, the analyses were performed by age (<2 years vs. ≥2 years). Furthermore, analyses were performed by time since exposure (<30 days vs. ≥30 days) to try to distinguish between a possible direct (i.e., causal) association (<30 days) and an association more likely to be related to shared risk factors (≥30 days).

All RRs were adjusted for sex and calendar period (6-month intervals from 1 May through 30 November and 1 December through 30 April of subsequent years, thus adjusting for possible seasonal effects). Age was adjusted using cubic splines based on 1-month intervals. In addition, RRs were adjusted for underlying chronic disease, total number of hospital contacts, and total duration of hospitalization, because preliminary analyses revealed that these factors confounded the observed associations. Correlations between monthly incidence rates of IPD and RSV infection were calculated using the Pearson R coefficient.

**Ethical approval.** The study was based on Danish registry data and was approved by the Danish Data Surveillance Authority (2006-41-6513).

**RESULTS**

In Denmark, there were 17,281 hospitalizations for RSV infection, 45,485 hospitalizations for non-RSV respiratory infections, and 7787 cases of IPD from 1 January 1996 through 1 July 2003. The median age at diagnosis of RSV infection was 6 months, whereas the median age at IPD diagnosis was 65 years. A total of 8928 (57%) of patients hospitalized with RSV infection and 3897 (50%) patients with IPD were male. During >7 million person-years of follow-up, 61 individuals experienced both hospitalization for RSV infection and IPD. Among these individuals, 41 (66%) had an underlying chronic disease.

**Temporal association.** On the population level, IPD incidence rates showed seasonal variation, with low rates during the summer and a fluctuating pattern throughout the rest of the year. The RSV infection season was from late October through March, with peak activity in mid-January (figure 1). As in earlier studies, a striking temporal correlation was found between hospitalization for RSV infection and IPD ($r = 0.55; P < .01$). This correlation was, however, just as strong—if not stronger—for hospitalization for non-RSV respiratory infection and IPD ($r = 0.65; P < .01$) (figure 1).

The seasonal correlation between RSV infection and IPD was age dependent. In children aged <2 years, we observed no seasonality of IPD; thus, the monthly incidence of IPD did not correlate with the monthly incidence of hospitalization for RSV infection ($r = .08; P = .41$) (figure 2).

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**Figure 1.** Monthly incidence rates of invasive pneumococcal disease (IPD) and hospitalization for respiratory syncytial virus (RSV) infection and non-RSV respiratory infection in Denmark, 1 January 1996–1 July 2003.
**Individual-level analyses.** Because, in this cohort, there were no hospitalizations for RSV infection among persons aged 10–15 years and no cases of IPD within 30 days after hospitalization for RSV infection in children aged 2–14 years, the individual-level analyses were limited to children aged <2 years. The RRs of IPD among Danish children aged <2 years who were hospitalized for RSV infection or non-RSV respiratory infection, by time since hospitalization, were compared with the RR of IPD in children without such a registration in table 1. Table 2 shows the results of opposite association: the RRs of hospitalization for RSV infection in Danish children aged <2 years who had IPD, compared with such children who did not have IPD.

**RSV infection preceding IPD.** Adjusted for age, sex, and calendar period, hospitalization for RSV infection or for non-RSV respiratory infection increased the risk of subsequent IPD both within and after 30 days of hospitalization among children aged <2 years. However, additional adjustment for chronic disease, total number of hospital contacts, and total duration of hospitalization before RSV infection or IPD had a statistically significant effect on the estimates. Thus, after additional adjustment, recent (<30 days) hospitalization for RSV infection increased the risk of subsequent IPD (adjusted RR, 7.1; 95% CI, 3.6–14.3). In addition, recent (<30 days) hospitalization for non-RSV respiratory infection increased the risk of subsequent IPD (adjusted RR, 4.5; 95% CI, 2.0–10.0). After the period of 30 days, no association was observed between hospitalization for RSV infection or non-RSV respiratory infection and subsequent IPD.

**IPD preceding RSV.** After adjustment for chronic disease, total number of hospital contacts, and total duration of hospitalizations before RSV infection or IPD, children with IPD did not have an increased risk of subsequent hospitalization for RSV infection, irrespective of the time between the 2 diseases. However, having IPD significantly increased the risk of a subsequent hospitalization for non-RSV respiratory infection both before and after the 30 days from the IPD event.

**DISCUSSION**

The present study examined the association between hospitalization for RSV infection or non-RSV respiratory infection and IPD. In short, we observed a temporal correlation between hospitalization for RSV infection or non-RSV respiratory infection and IPD at a population level, but the temporal correlation was only present among individuals aged ≥2 years. At an individual level, recent RSV infection increased the risk of IPD among children aged <2 years.

Our study design is unique in that we examined the associations both ways (i.e., the risk of bacterial infection after viral infection and the risk of viral infection after bacterial infection). Moreover, we examined the associations between viral and bacterial infections at an individual level in addition to the population-level analyses. The observed associations between hospitalization for RSV infection or non-RSV respiratory infection...
and IPD could be explained by either the exposure predisposing to the outcome (i.e., causality) or common determinants of the 2 diseases.

In our population, both being hospitalized for RSV infection or non-RSV respiratory infection and experiencing IPD were rare events that mostly occurred in chronically ill children. Thus, in our study population, 20% of the children with IPD and nearly 70% of the individuals experiencing both RSV infection and IPD had received a prior hospital diagnosis of chronic disease (data not shown). Chronically ill children are known to acquire severe, symptomatic infections of any kind because of genetic disposition to immunodeficiencies, immunosuppressive treatment, or the increased risk of nosocomial infections among frequently hospitalized children. This underlines the importance of common risk factors as an explanation of the association between the RSV infection and IPD.

**Hospitalization for non-RSV respiratory infection.** We were unaware of which pathogens caused the non-RSV respiratory infections. Recent studies have shown that the ELISA-based assays used for RSV detection in the present study have sensitivities as low as 50%, compared with newer PCR-based techniques, and it is plausible that a substantial part of the RSV-negative test results were false-negative. Besides RSV, a broad array of respiratory pathogens can cause illness with the same symptoms as RSV infection. Most pathogens were probably of viral origin; however, some might have been bacterial (e.g., some infections may have been pneumococcal infections) [24–26]. Although it was difficult to draw conclusions concerning the group of patients who were hospitalized for non-RSV respiratory infection, we included the group to determine whether RSV infection per se increased the risk of IPD or whether other airway infections also increased the risk of IPD.

**Temporal association.** On a population level, we observed a strong temporal correlation between hospitalization for RSV infection or non-RSV respiratory infection and IPD, indicating that airway infections, including infections other than RSV infection, may be associated with IPD. However, the pattern was age dependent, and no temporal association was found among children aged <2 years, among whom hospitalization for RSV infection was most frequent.

**Individual-level analyses.** Because the present and previous studies [8–10] also have shown different temporal correlation patterns dependent on the age groups studied, we decided to analyze the associations on an individual level separately.

### Table 1. Rate ratios of respiratory syncytial virus (RSV) infection preceding invasive pneumococcal disease (IPD; RSV exposure and IPD outcome) among Danish children aged <2 years.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of RSV and IPD events</th>
<th>No. of IPD events</th>
<th>Person-years</th>
<th>Rate ratio (a) (95% CI)</th>
<th>Rate ratio adjusted for comorbidity(b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive RSV test result &lt;30 days before IPD</td>
<td>9</td>
<td>411</td>
<td>1,047,591</td>
<td>16.3 (8.3–31.7)</td>
<td>7.1 (3.6–14.3)</td>
</tr>
<tr>
<td>Hospitalization for RSV infection</td>
<td>7</td>
<td>363</td>
<td>1,039,297</td>
<td>11.0 (5.2–23.2)</td>
<td>4.5 (2.0–10.0)</td>
</tr>
<tr>
<td>Positive RSV test result ≥30 days before IPD</td>
<td>15</td>
<td>411</td>
<td>1,047,591</td>
<td>2.4 (1.4–4.0)</td>
<td>1.2 (0.7–2.0)</td>
</tr>
<tr>
<td>Hospitalization for non-RSV respiratory infection</td>
<td>23</td>
<td>363</td>
<td>1,039,297</td>
<td>3.2 (2.1–4.8)</td>
<td>1.3 (0.8–2.0)</td>
</tr>
</tbody>
</table>

**NOTE.** \(P < .01\) for all comparisons.  
\(a\) Rate ratios were adjusted for sex, age, and calendar period.  
\(b\) Rate ratios were adjusted for sex, age, calendar period, underlying chronic disease, total number of hospital contracts, and total duration of hospitalizations before RSV infection or IPD.

### Table 2. Rate ratios of invasive pneumococcal disease (IPD) preceding respiratory syncytial virus (RSV) infection (IPD exposure and RSV outcome) among Danish children aged <2 years.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of IPD and RSV events</th>
<th>No. of RSV events</th>
<th>Person-years</th>
<th>Rate ratio (a) (95% CI)</th>
<th>Rate ratio adjusted for comorbidity(b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPD &lt;30 days before positive RSV test result</td>
<td>34</td>
<td>21,068</td>
<td>1,034,702</td>
<td>5.0 (3.5–7.0)</td>
<td>1.5 (1.0–2.3)</td>
</tr>
<tr>
<td>Hospitalization for RSV infection</td>
<td>6</td>
<td>15,057</td>
<td>1,041,001</td>
<td>5.4 (1.7–16.6)</td>
<td>2.2 (0.7–6.8)</td>
</tr>
<tr>
<td>Hospitalization for non-RSV respiratory infection</td>
<td>23</td>
<td>21,068</td>
<td>1,034,702</td>
<td>5.3 (3.5–8.0)</td>
<td>2.2 (1.5–3.3)</td>
</tr>
</tbody>
</table>

**NOTE.** \(P < .01\) for all comparisons.  
\(a\) Rate ratios were adjusted for sex, age, and calendar period.  
\(b\) Rate ratios were adjusted for sex, age, calendar period, underlying chronic disease, total number of hospital contracts, and total duration of hospitalizations before RSV infection or IPD.
among children aged <2 years and among children aged 2–14 years. However, we found no cases of IPD within 30 days after hospitalization for RSV infection among the children aged 2–14 years and, thus, limited the analyses to children aged <2 years.

RSV infection preceding IPD. On an individual level, recent hospitalization for RSV infection increased the risk of IPD during early childhood. Because there was not an increased risk of IPD after the period of 30 days and the analysis was further adjusted for underlying chronic disease and number and duration of hospitalizations, this finding pointed at a direct effect of recent hospitalization for RSV infection on the risk of IPD among young children. Recent hospitalization for non-RSV respiratory infection also increased the risk of IPD, and again, the increased risk was limited to the 30 days after hospitalization. Because both hospitalization for RSV infection and hospitalization for non-RSV respiratory infection were found to increase the risk of IPD, we speculate whether the observed associations were attributable to a direct effect of the pathogens or to an effect caused by any hospitalization for severe airway infection.

The association between hospitalization for RSV infection or non-RSV respiratory infection and IPD might be explained by the recent study by Madhi et al. [6, 7] that suggested that the severity of viral airway infections might depend on increased invasiveness of colonizing bacteria during the acute viral infection. Children develop IPD from bacteria colonizing the nasopharynx [27], and IPD might signal their risk of being heavily colonized. This would increase their risk of both severe, symptomatic airway infection when virally infected and subsequent IPD. As in earlier studies, including studies about influenza [9] and human metapneumovirus [7], we observed an increased risk of IPD after non-RSV airway infection. We concluded that both recent hospitalization for RSV infection and recent hospitalization for non-RSV respiratory infection, probably through a direct effect, increased the risk of IPD among young children.

IPD preceding RSV infection. IPD increased the risk of hospitalization for non-RSV respiratory infection at any time after IPD. The analysis was adjusted for underlying chronic disease and number and duration of hospital contacts, and although the association could be attributable to residual confounding, this finding may have other biological or nonbiological explanations. The studies by Madhi et al. [6, 7] illustrate that heavily bacterially colonized children are more prone to severe, symptomatic infection when virally infected. Thus, children who experienced IPD were also probably at increased risk of bacterial nasopharyngeal colonization after the IPD episode, increasing their risk of subsequent severe viral infection. Alternatively, the finding might reflect the increased level of care among parents and health care workers for a child after a severe, life-threatening infection, and the associations may be biologically unrelated.

Study limitations. IPD was a rare event in the Danish population, and having both IPD and RSV infection was even less likely. Although we conducted a nationwide study during a 7-year period, the individual-level analysis was often based on few numbers of patients, and the absolute level of the RRs should be interpreted with caution. Denmark is a high-income country, and our findings may not represent the associations between viral airway infection and IPD in low-income populations with a different infection frequency and different bacterial colonization patterns.

Summary. The present study involving the Danish population used nationwide surveillance data to examine the associations between hospitalization for RSV infection or non-RSV respiratory infection and subsequent IPD in children aged <2 years.

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Potential conflicts of interest. All authors: no conflicts.

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