We assessed the seasonality of viral lower respiratory tract infections (V-LRI), bacteremic pneumonia, nonbacteremic pneumonia and nonpneumonia invasive pneumococcal diseases (IPD) in the pre-PCV era. Both bacteremic and nonbacteremic pneumonia seasonality peaked in winter, coinciding with V-LRI seasonality, whereas non-pneumonia IPD peaked in autumn before V-LRI increase, suggesting different pathogenesis.

**Keywords.** seasonality; bacteremic pneumonia; viral lower respiratory infections; invasive pneumococcal diseases.

Bacteremic community-acquired pneumonia (CAP) accounts for 25%–35% of all invasive pneumococcal diseases (IPD) cases in young children [1]. However, in most CAP episodes, no pathogen can be isolated, and only 1%–6% of all episodes are blood-culture positive, most frequently with *Streptococcus pneumoniae* [2].

A previous observation suggested that in children, seasonality of bacteremic CAP (peaking in winter) was triggered by viral lower respiratory-tract infections (V-LRI), mainly respiratory syncytial virus (RSV), whereas seasonality of nonpneumonia IPD (peaking in autumn) was primarily driven by increased nasopharyngeal pneumococcal transmission [3].

In Israel, several ongoing, prospective, independent, active surveillance studies are conducted on IPD (pneumonia and nonpneumonia) [4], CAP, and V-LRI in children <5 years.

Our aim was to assess: (1) Whether the seasonality of hospital visits due to bacteremic and nonbacteremic CAP is similar and associated with V-LRI; and (2) whether seasonality of nonpneumonia IPD is indeed different from that of CAP and V-LRI.

**METHODS**

Data were obtained from 3 different ongoing, prospective, population-based, active surveillance studies in Israeli children <5 years: (1) Nationwide IPD surveillance; (2) hospital visits due to CAP in southern Israel; and (3) hospital visits due to V-LRI (RSV and influenza virus) in southern Israel. All 3 studies were approved by the national and the institutional ethics committees.

**Nationwide IPD Surveillance**

**Study Design**

The detailed description of data collection, vaccine uptake evaluation methods, and bacteriology were previously published [5]. Briefly, the study population consisted of all Israeli children <5 years. The study has been conducted in all 27 medical centers routinely obtaining cerebrospinal fluid (CSF) and blood cultures from children.

**Case Definition**

An IPD episode was defined as an illness episode during which *S. pneumoniae* was isolated from blood, CSF, or both. A bacteremic pneumonia episode was defined as an illness episode diagnosed as pneumonia by the treating physician during which *S. pneumoniae* was isolated from blood. A nonpneumonia IPD episode was defined as an IPD episode excluding bacteremic pneumonia episodes (mainly sepsis/bacteremia and meningitis).

The majority of cases did not have pleural effusion/empyema. However, the exact number of cases with pleuropneumonia could not be ascertained.

**Hospital Visits Due to CAP in Southern Israel**

**Setting**

The Soroka University Medical Center (SUMC) is the only hospital in the Negev district of southern Israel, providing primary and referral health services to the entire region population. Over
95% of the children living in the region are born and served by the SUMC, enabling incidence figures calculations.

**Study Design**

The detailed description of this study, initiated in 2002, was previously reported [6]. All children <5 years treated at the SUMC with a radiologically diagnosed CAP were included. Chest radiographs were analyzed, and the diagnosis of alveolar pneumonia was determined according to the World Health Organization definitions [6].

**Hospital Visits Due to V-LRI (RSV and Influenza Viruses) in Southern Israel**

**Study Population**

We prospectively enrolled children <5 years old admitted with LRI to the SUMC’s pediatric wards since 2004. All children tested for viruses (specifically, RSV and influenza) by nasal wash were included.

**Viral Detection**

Nasal wash specimens sent to the Clinical Virology Laboratory within 24 hours of admission were diluted with Roswell Park Memorial Institute medium, as previously described [7]. Samples were studied for the presence of RSV and influenza viruses, by direct immunofluorescence assay, tissue culture, or by polymerase chain reaction.

In previous studies conducted at the SUMC, viruses were detected in 57% of LRI [7] and 46.9% of CAP episodes [8].

**Statistical Analyses**

Incidence rates were calculated by dividing the monthly number of episodes by the total number of at-risk children. For V-LRI and nonbacteremic CAP episodes we used the monthly figures among children <5 years presenting to the SUMC and divided them by the at-risk population <5 years in southern Israel (figures presented per 1000). For nonpneumonia IPD and bacteremic pneumonia, we used the nationwide figures of IPD in children <5 years and divided them by the overall nationwide at-risk population <5 years (figures are presented per 100 000).

Seasonality (proportion of episodes per season) was calculated by dividing the 3-month periods (summer: June through August; autumn: September through November; winter: December through February; and spring: March through May) rates of each entity by its total annual rate.

**RESULTS**

Both bacteremic pneumonia and CAP rates peaked in the winter months, in each of the 4 pre-pneumococcal conjugate vaccine (PCV) years (Figure 1). The mean rate of bacteremic pneumonia in Israeli children <5 years (per 100 000) increased from 2.67 and 2.80 in summer and autumn, respectively, to 6.30 in winter, and then declined to 4.63 in spring (Supplementary Table 1). Similarly, the mean rate of CAP in children <5 years in southern Israel (per 1000) increased from 1.92 and 1.99 in summer and autumn, respectively, to 5.95 in winter, and then declined to 3.66 in spring. Overall, 38% and 44% of all bacteremic and nonbacteremic pneumonia episodes, respectively, were observed in winter.

The seasonality of LRI caused by both RSV and influenza-virus coincided with that of bacteremic and nonbacteremic pneumonia, peaking in winter, in each of the 4 pre-PCV years (Figure 1). RSV-LRI mean seasonal rate in children <5 years in southern Israel (per 1000) increased from 0.01 and 0.09 in summer and autumn, respectively, to 5.64 in winter, and then declined to 1.21 in spring. Similarly, influenza-LRI mean seasonal rate (per 1000) increased from ≤0.01 in both summer and autumn to 0.41 in winter, and then declined to 0.17 in spring. Overall, 81% of RSV and 69% of influenza episodes were detected in winter.

In contrast to both bacteremic and nonbacteremic pneumonia (both started peaking in winter, coinciding with V-LRI), the seasonality of nonpneumonia IPD started peaking in autumn (before V-LRI), in each of the 4 pre-PCV years. The mean seasonal incidence of nonpneumonia IPD in Israeli children <5 years (per 100 000) increased from 5.10 in summer to 10.24 in autumn, and remained 10.32 and 9.28 in winter and spring, respectively. Overall, 15%, 29%, 30%, and 27% of all nonpneumonia IPD episodes occurred in summer, autumn, winter, and spring, respectively.

No significant differences between the seasonality of different pneumococcal serotypes causing both pneumonia and nonpneumonia IPD were found (data not shown here).

**DISCUSSION**

The seasonality observed in nonbacteremic CAP in this study was similar to that of bacteremic pneumococcal pneumonia, both coinciding with viral-LRI, peaking in winter. In contrast, nonpneumonia IPD rates started peaking in autumn. Our findings concur with a previous report by Weinberger et al, comparing the seasonality of nonpneumonia IPD and bacteremic pneumococcal pneumonia, with similar findings [3]. The editorial commentary to that study called for confirmation by other studies in different settings with different populations [9]. Furthermore, to the best of our knowledge, our report is the first to show overlapping seasonality of bacteremic and nonbacteremic pneumonia, both contrasting to nonpneumonia IPD. Weinberger et al suggested that the seasonality of invasive pneumonia could be triggered by viral pathogens, whereas seasonality of nonpneumonia IPD might be primarily driven by increased pneumococcal nasopharyngeal transmission. The increased pneumococcal carriage and transmission could be related to the coinciding start of the school year. The parallel pattern of RSV...
and influenza infections and pneumonia seasonality in our study support this notion. Our data suggest that the main driver of both bacteremic and nonbacteremic pneumonia is RSV, since RSV rates were much higher than those of influenza virus or other tested viruses [7]. Notably, in a previous study, the seasonality of other V-LRI, including human metapneumovirus, parainfluenza, and adenovirus, exhibited similar pattern, with >60% of all episodes occurring in winter [7].

We speculate that when RSV infection and pneumococcal colonization coincide, a synergetic effect of the potential
increased density of colonization (facilitating pneumococcal aspiration) and the lung inflammatory response (promoting pneumococcal proliferation in the lung tissue and systemic invasion) results in increased rates of both bacteremic and nonbacteremic CAP [10]. In addition, the co-presence of S. pneumoniae and RSV may increase pneumococcal virulence. A recent study demonstrated that following the co-incubation with RSV, pneumococci demonstrated a significant increase in the inflammatory response and markedly increased its virulence in a mouse pneumonia model [11]. This was associated with a significant up-regulation in the expression of key pneumococcal virulence genes, including the pneumolysin gene.

In addition to difference in seasonality, we found in a previous study that when comparing bacteremic pneumonia to non-pneumonia IPD, age-distribution and serotype differences were significant, leading to a differential impact after PCV7 and PCV13 introduction to the national immunization plan [4]. The current findings coupled with those previously published strongly suggest that pneumococcal pneumonia and nonpneumococcal IPD have, at least in part, different pathogenesis.

We did not assess other factors that may affect seasonality, like temperature. However, a previous study [12] did not detect any significant differences in monthly temperature, humidity, precipitation, or wind across the study period that might explain the seasonal patterns in CAP.

In summary, our findings support a common pathogenesis for bacteremic pneumonia and CAP, both associated with V-LRI. The fact that nonpneumonia IPD seasonality significantly differed from that of other studied entities suggests a different pathogenesis.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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