Spectrum of Respiratory Viruses in Children With Community-acquired Pneumonia

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Background: Community-acquired pneumonia (CAP) remains a significant cause for childhood morbidity worldwide. We designed a study with the objective of describing the frequency of respiratory viruses, especially rhinovirus (RV), human metapneumovirus (HMPV) and human bocavirus (HBoV) in hospitalized children with CAP.

Methods: A 6-year prospective study was conducted in children <14 years old admitted to the Pediatrics Department of the Severo Ochoa Hospital (Spain) with CAP. We studied the frequency of 16 respiratory viruses in nasopharyngeal aspirates. Clinical characteristics of respiratory syncytial virus (RSV)-only infections were compared with those of RV, HMPV and HBoV single infections.

Results: A viral pathogen was identified in 649 (73.4%) of 884 hospitalized children with CAP. Viral coinfections were detected in 30%. The rate of viral detection was significantly greater in infants <18 months (83%) than in older children (67%) ($P < 0.001$). The most frequently detected virus was RSV with 41.6% of positive patients followed by RV (26.2%), HBoV (17.8%), adenovirus (17.8%), HMPV (7%) and parainfluenza (7%). RSV was the most frequent virus in children <18 months, but RV was most common in the eldest group ($P < 0.001$). After stratifying by age, we found some significant differences among RSV, RV, HBoV and HMPV-associated infections.

Conclusions: The high prevalence of viral infections supports the role of respiratory viruses, mainly RSV, RV, HBoV and HMPV in CAP of children requiring hospitalization. These findings help us to understand the etiologic disease burden and to guide research and public health policy.

Key Words: human bocavirus, human metapneumovirus, rhinovirus, respiratory syncytial virus, pneumonia

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Community-acquired pneumonia (CAP) is one of the leading causes of acute respiratory morbidity among children all over the world. In most developing countries, CAP is associated with many hospitalizations and deaths in children <5 years old.[1] Moreover, CAP has a considerable effect on the health-care system of western countries despite the development of antimicrobial therapy and effective vaccines.[2] Since the introduction of polymerase chain reaction (PCR) on the diagnosis of respiratory tract infections, viral pathogens are increasingly recognized as playing a major role in the etiology of CAP in preschool children.[3] However, establishing the cause of pneumonia remains challenging, because distinguishing possible prolonged shedding or colonization from active infection can be difficult.

The objectives of the present study were first to investigate the presence of respiratory viruses, especially rhinovirus (RV) and the newly discovered human metapneumovirus (HMPV) and human bocavirus (HBoV), in respiratory specimens taken from radiologic diagnosed CAP children; and second to compare the demographic, clinical and laboratory features of children with virus-associated CAP versus children without viral detection; single infections versus dual/multiple infections; as well as different respiratory viruses versus respiratory syncytial virus (RSV).

SUBJECTS AND METHODS

Clinical Assessment

Between September 2004 and July 2010, all consecutive hospitalized children <14 years old with CAP were prospectively evaluated in the Pediatrics Department of the Severo Ochoa Hospital (Madrid, Spain). At admission, the diagnosis was based on respiratory complaints (rhinorrhea, cough or difficulty in breathing) with fever and pulmonary infiltrates compatible with pneumonia in the chest radiograph. A senior radiologist, blinded to clinical and laboratory findings, reviewed all chest radiographs and assigned a standardized description as proposed by the World Health Organization working group[4] according to which the presence of consolidation or pleural effusion with parenchyma infiltrate defined pneumonia.

All patients were evaluated by an attending physician. During the hospital stay and as part of the study, a physician completed a standardized form with the following variables: age, sex, history of prematurity and underlying chronic diseases, need for oxygen therapy assessed by transcutaneous oxygen saturation, fever (temperature ≥38ºC), presence of infiltrate in radiographs, administration of antibiotic therapy, duration of hospital stay, total white blood cell (WBC) count, C-reactive protein (CRP) serum values and result of blood culture when it was done. Oxygen therapy was provided to achieve oxygen saturation ≥94%. The study was approved by The Medical Ethics Committee. Informed consent was obtained from parents or legal guardians.

Virus Detection

Specimens from patients consisted of nasopharyngeal aspirates (NPA) taken from each patient at admission (Monday through Friday). Each specimen (1 for each patient) was sent for virologic investigation to the Influenza and Respiratory Virus Laboratory at the National Microbiology Center (ISCIII, Madrid, Spain). Specimens were processed within 24 hours after collection. Upon receipt of NPAs, 3 aliquots were prepared and stored at −70ºC. Both the reception and the NPA sample aliquoting areas were separate from those defined as working areas.

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PCR Methods for Detection of 16 Respiratory Viruses

Three reverse transcription (RT)-nested PCR assays were performed to detect a total of 16 respiratory viruses. In these assays, RT and first amplification round were carried out in a single tube using the Qiagen OneStep RT-PCR kit (Qiagen, Hilden, Germany). Influenza A, B and C viruses were detected by using a previously described method including only the primer sets to amplify influenza viruses in a multiplex PCR assay.[5] A second multiplex PCR was used to detect parainfluenza viruses 1 to 4, human coronaviruses 229E and OC43, enteroviruses and RVs.[6] Presence of RSV-A and B types, HMPV, HBoV and adenoviruses were investigated by a third multiplex RT-nested PCR method.[7]

Prevention of PCR Contamination

Because of the high sensitivity of nested PCR, precautions were taken to prevent contamination of reaction tubes with previously amplified product or target RNA or DNA from other specimens and controls. An aliquot of the respiratory specimens, preparation of reagents, processing of samples and nested-PCR were performed in safety cabinets located in separated laboratories, all away from the area in which amplified products were analyzed. Each cabinet was equipped with an independent batch of reagents, micropipette sets, sterile reagent tubes and filtered pipette tips.

Statistical Analysis

Values were expressed as percentages for discrete variables or as mean and standard deviation for continuous variables. Clinical characteristics of patients with positive and negative viral detection were compared. Clinical characteristics and laboratory variables were compared using the Student *t* test, the Mann-Whitney *U* test, the χ^2 test and Fisher exact test. The Mantel–Haenszel χ^2 test was used for stratified analyses. To avoid confusion, patients were stratified as being younger or equal to or older than 18 months of age to better analyze clinical and virologic features. A 2-sided value of $P < 0.05$ was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

The study population consisted of 1034 hospitalized children <14 years old with CAP. A total of 884 patients (51% males) were analyzed; 150 parents denied initial consent or refused NPA collection after the initial agreement. The mean age of the group was 28.5 months (median: 18 months); 112 (12.6%) were born prematurely. Most patients, 746 (84%), had fever ≥38ºC and the average temperature at admission was 39ºC. Antibiotic therapy was prescribed in 500 cases (56%). Four hundred seventy-four children had a blood culture taken on admission. Twenty of them (2.2%) had a positive blood culture [*Streptococcus pneumoniae* (19), *Moraxella catarrhalis* (1)]. Three out 25 (12%) children who presented with pleural effusion had a positive blood culture. Four hundred sixty-five patients (52%) required supplemental oxygen therapy during a mean of 3 days. The average duration of hospitalization was 4.8 days ranging from 1 to 25 days. Thirty-two (3.6%) children needed to be transferred to the pediatric intensive care unit; one of them, with severe asthma, encephalopathy and influenza A (H1N1)-associated pneumonia, died.

There was a large variation in the number of monthly CAP-associated hospitalizations, but a clear seasonal pattern with 2 peaks could be observed; a major autumn peak in November and December and a second minor peak from February to April, with a maximum in March. The monthly distribution of viral positive and negative CAP was almost identical. The seasonality of specific viral detection in pediatric patients hospitalized with CAP was similar to that detected in our country in other respiratory infections (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/B161).[8]

Viral Detection

At least 1 potential viral pathogen was identified in 649 children (73.4%). The frequency of viral detection in infants <18 months was significantly higher than in older children: 83% versus 67%, $P < 0.001$, odds ratio (OR) = 1.773, 95% confidence interval (CI): (1.395–2.253). Specific viruses detected in the total population of 884 children are listed in Table 1, in descending order of frequency. The most frequently detected virus was RSV (41.6% of positive patients; RSV-A = 167, RSV-B = 60, untyped = 43), followed by RV (26.2%), HBoV (17.8%), adenovirus (17.8%) and parainfluenza (5.3%; n = 47: type 1 = 19, type 2 = 10, type 3 = 8 and type 4 = 10). Some differences were found when viral detection was stratified by age (Table 2).

Out of positive samples, 454 (70%) were single virus infections whereas 195 (30%) were dual or multiple viral infection. Coinfections were also more frequent in the youngest patients (34.5% versus 24%, $P = 0.004$, OR = 1.312, 95% CI: (1.100–1.564). The most frequent virus associated with viral coinfection was HBoV (82/116, 70.7%), followed by adenovirus (59/116, 51%) and RV (76/170, 45%).

TABLE 1. Respiratory Viruses Associated With Pneumonia in Eight Hundred Eighty-four Hospitalized Children

Total Virus Detections* (n = 831)	n (%)†	Single Infections, n (%)‡ (n = 454)
Respiratory syncytial virus	270 (30.5)	178 (66)
Rhinovirus	170 (19.2)	94 (55.2)
Human bocavirus	116 (13.1)	31 (26.7)
Adenovirus	116 (13.1)	57 (50)
Parainfluenza virus	47 (5.3)	28 (59.5)
Human metapneumovirus	46 (5.2)	30 (65.2)
Influenza virus	45 (5)	32 (71.1)
Coronavirus	12 (1.3)	2 (16.6)
Citomegalovirus	4 (0.5)	2 (50)

*Eight hundred eighty-four patients, 454 single infections, 195 multiple infections, 235 negatives. Some of the 649 virus-positive patients had multiple viruses.
†Percentage of 884 patients.
‡Percentage of single infection from each respiratory virus.

TABLE 2. Etiology of CAP in Positive-virus Children Stratified by Age (Younger and Older Than 18 Months)

	Age <18 months (n = 284)	Age ≥18 months (n = 365)	*P*
Respiratory syncytial virus	170 (59.8%)	100 (27.3%)	<0.001
Rhinovirus	56 (19.7%)	114 (31.2%)	0.002
Human bocavirus	59 (19.7%)	57 (15.6%)	0.060
Adenovirus	46 (16.1%)	70 (19.1%)	0.436
Human metapneumovirus	26 (9%)	20 (5.4%)	0.078
Parainfluenza virus	22 (7.7%)	30 (8.2%)	0.499
Influenza virus	13 (4.5%)	32 (8.7%)	0.035
Coronavirus	5 (1.7%)	7 (1.9%)	0.875
Citomegalovirus	0 (%)	2 (0.5%)	0.1210

Positive Viral CAP Versus Negative Group

Regarding clinical characteristics, virus-positive and virus-negative CAP episodes were compared stratifying both groups by age, younger and equal to or older than 18 months. Irrespective of age, patients with documented viral infections were more likely to present hypoxia [58% versus 36%, $P < 0.001$, OR = 1.274, 95% CI: 1.172–1.385] and wheezing [53% versus 31%, $P < 0.001$, OR = 1.267, 95% CI: (1.170–1.372)]. Antibiotic treatment was prescribed less frequently in viral-positive patients [51% versus 70%, $P < 0.001$, OR = 0.820, 95% CI: (0.758–0.886)] but only when they were >18 months. No differences could be found regarding the length of hospital stay, the duration of oxygen therapy or the presence of pleural effusion between virus-positive and virus-negative CAP children.

Multiple Viral Infections Versus Single Group

Clinical characteristics of children with CAP associated with single and dual/multiple viral infections were also compared. Overall, coinfections presented hypoxia [65% versus 56%, $P < 0.046$, OR = 1.294, 95% CI: (1.001–1.6)] and wheezing [62% versus 50%, $P < 0.006$, OR = 1.418, 95% CI: (1.102–1.826)] more frequently than single infections; although coinfections needed shorter oxygen therapy (mean: 2.5 ± 1.9 days versus 3.3 ± 2.5 days, $P = 0.002$) and a shorter hospital stay than single infections (4.6 ± 2.9 days versus 5.0 ± 2.8, $P = 0.06$). However, after stratifying by age, only the length of oxygen therapy remained significantly shorter in coinfections in <18 months of age (2.6 ± 1.9 versus 3.4 ± 2.3 days, $P = 0.017$). No other significant differences were found.

Clinical Findings Associated With the Presence of RSV, HBoV, RV and HMPV Single Infections

CAP episodes of 454 children were associated with a single virus. RSV was present in 178 of these patients (38.2%). As RSV was the most common virus detected, patients with RV (n = 94, 20%), HBoV (n = 31, 6.7%) and HMPV (n = 30, 5.6%)-associated CAP were compared with those with RSV-associated CAP. For this analysis, patients were stratified in 2 groups, younger (Table 3) and ≥18 months of age (Table 4).

Bacterial Infections

Twenty patients had a positive blood culture: *S. pneumoniae* (19/20), *M. catarrhalis* (1/20). Most cases (16/20) were detected between October and April. In 14 of them (70%), at least 1 virus was detected simultaneously, such as influenza (4/14), RSV (4/14) and RV (3/14). Two patients needed ICU admission; in both of them coinfection with RSV and influenza respectively were detected.

Two hundred fifty-three (54%) patients <24 months had a blood culture taken on admission versus 221 patients in the elder group (46.6%). Patients <24 months were less likely to have bacteremia than older children [$P = 0.06$, OR = 0.437, 95% CI:

TABLE 3. Clinical Characteristics of CAP Associated With Single Detection of RSV Compared With RV, HBoV, HMPV in Children Younger Than 18 Months of Age

Clinical Feature	RSV (n = 101)	RV (n = 23)	HBoV (n = 11)	HMPV (n = 18)	*P*
Male	49(48.5%)	18 (78.3%)	7 (63.6%)	8 (44.8%)	0.01
Prematurity	9 (8.9%)	1 (4.3%)	2 (18.2%)	3 (17.6%)	NS
Temperature >38°C	77 (76.2%)	14 (60.9%)	9 (81.8%)	15 (83.3%)	NS
Hypoxia (SatO2 <95%)	73 (73%)	11 (47.8%)	9 (81.8%)	12 (66.7%)	0.02
Wheezing	95 (94.1%)	18 (78.3%)	10 (90.9%)	3 (25%)	0.01
Antibiotic treatment	25 (24.9%)	12 (52%)	6 (54.5%)	3 (27.3%)	0.03
Highest temperature	38.7 ± 0.6	38.2 ± 1.1	38.8 ± 0.8	39.0 ± 0.67	NS
Leucocytes (cells/mm^3)	12427 ± 4629	21453 ± 10299	12196 ± 3875	12402 ± 5104	0.001
Serum C-reactive protein (mg/L)	32.2 ± 46.1	81 ± 109	35.7 ± 30.7	35 ± 33	0.05
Age (months)	6.3 ± 4.6.7	6 ± 4.7	11.3 ± 3.9	10.0 ± 3.9	0.001
Hospital stay (days)	5.7 ± 2.7	4.7 ± 2.3	5.5 ± 3.6	5.3 ± 2.5	NS
Fever duration(days)	3.2 ± 2.1	3.4 ± 2.4	3.8 ± 3.2	3.4 ± 1.6	NS
Hypoxia duration (days)	3.6 ± 2.5	3.7 ± 2.6	2.8 ± 2.9	3.3 ± 1.2	NS

NS indicates not statistically significant.

TABLE 4. Clinical Characteristics of CAP Associated With Sole Detection of RSV Compared With RV, HBoV and HMPV in Children Older Than 18 Months of Age

Clinical Feature	RS (n = 77)	RV (n = 75)	HboV (n = 20)	hMPV (n = 12)	*P*
Male	36 (46.8%)	36 (48%)	8 (40%)	7 (58%)	>0.05
Prematurity	15 (19.5%)	12 (15.8%)	1 (5%)	2 (17%)	>0.05
Temperature >38°C	68 (88.3%)	59 (77.6%)	19 (95%)	12 (100%)	0.05
Hypoxia (SatO2 <95%)	58 (75.3%)	27 (35.5%)	6 (30%)	8 (67%)	<0.001
Wheezing	23 (30%)	19 (25%)	4 (20%)	3 (25%)	>0.05
Antibiotic treatment	36 (46.8%)	45 (59.2%)	16 (80%)	5 (42%)	0.008
Highest temperature	38.9 ± 0.7	39.1 ± 0.8	39.3 ± 0.7	39.0 ± 0.4	0.020
Leucocytes (cells/mm^3)	12427 ± 4629	19338 ± 8547	19288 ± 8626	11661 ± 4285	0.001
Serum C-reactive protein	32.2 ± 46.1	105 ± 109	93.2 ± 83.5	40.3 ± 55.9	0.001
Age (months)	21.4 ± 14.7	43.1 ± 30.1	44.0 ± 28.7	24.2 ± 14.0	0.001
Hospital stay (days)	5.8 ± 3.3	3.9 ± 1.7	4.0 ± 3.1	4.3 ± 2.5	0.028
Fever duration (days)	4.1 ± 5.7	3.6 ± 2.5	3.7 ± 2.2	4.0 ± 2.0	NS
Hypoxia duration (days)	3.6 ± 2.6	2.4 ± 2.3	2.0 ± 2.0	2.8 ± 1.9	0.05

NS indicates not statistically significant.

(0.180–1.063)]. Two hundred fifty-three (54%) and some clinical characteristics exhibited by the youngest children suggest that viral infections are more frequent in this group: Viral detection was more frequent [81.6% versus 61%, $P < 0.001$, OR = 1.611, 95% CI: (1.372–1.891)], also they had less frequent fever ≥38º [80% versus 90%, $P < 0.001$, OR = 0.766, 95% CI: (0.684–0.857)], received less antibiotic treatment [42.3% versus 77.4%, $P < 0.001$, OR = 0.573, 95% CI: (0.514–0.638)] and had more frequent wheezing [63% versus 23%, $P < 0.001$, OR = 1.898, 95% CI: (1.690–2.132)].

Clinical features significantly associated with bacteremia were pleural effusion [$P = 0.011$, OR = 4.167, 95% CI: (1.349–12.870)] and absence of wheezing [$P = 0.038$, OR = 3.294, 95% CI: (0.985–11.021)]. Analysis of laboratory data showed that overall children with bacterial pneumonia had higher inflammatory indices: CRP (164 mg/L versus 80 mg/L, $P < 0.001$) and total WBC count (20,309 versus 15,775 cells/mm^3, $P = 0.010$). The ability of CRP and WBC count to differentiate patients with and without bacteremia was assessed with receiver operating characteristic curve analysis. The area under the receiver operating characteristic curve for CRP was 0.685 (0.558–0.811, $P = 0.004$) and for WBC count 0.637 (0.536–0.737, $P = 0.034$). A CRP value of 23.5 mg/L had a sensitivity of 81% and a specificity of 37%. A WBC count of 12,670 cells/mm^3 had a sensitivity of 81% and a specificity of 42%.

DISCUSSION

The frequency of viral detection in 884 CAP-hospitalized children was 73.4% in this prospective study. This figure was even higher in children <18 months of age, where the rate of viral detection reached 83%. Our results confirm that respiratory viruses play a key role in CAP episodes, not only in infants but also in older children. As far as we know, this is the highest frequency of respiratory virus detection described until now in CAP-children. Besides the use of a panel of very sensitive PCR assays for a full range of respiratory viruses, described by our group elsewhere,[5–7,9] the major strength of our study is the enrollment of a high number of patients, 884, over almost 6 full calendar years. This wide inclusion period reduces potential biases toward seasonal differences in respiratory virus circulation. Therefore, our results may quite accurately reflect the relative contribution of each respiratory virus to CAP episodes in hospitalized children.

Several studies, in which the viral cause of pediatric-CAP had been searched for by PCR, have been published.[3,10–16] Evidence of viral infection was recorded in 49% of cases (range 43–67). In those studies, RSV was the most frequently detected virus. Our results confirm the main role of RSV in pediatric CAP and also show that viral etiology of CAP changes with age. In fact, although in our series RSV was the most prevalent virus in very young children, RV was the most frequent in children ≥18 months old. RV infections are increasingly seen among children with CAP, partly explainable by the use of new sensitive PCR techniques.[12,17] RV had been considered a benign and sole upper airway pathogen for a long time, but it has been shown to infect lower respiratory tract cells and induce production of interleukin-6, -8 and -16 and regulated upon activation, normal T-cell expressed and secreted chemokine as well as being cytotoxic to cultured respiratory epithelium.[18] RV has also been highly detected in bronchiolitis[7,19] and asthma exacerbations[8,20] in infants and children. However, as most respiratory viruses, RV may be present in asymptomatic individuals,[21] causing doubts about its pathogenic role. Recently, Jansen et al[22] reported a quantitative PCR assay showing that cutoff values for clinical relevance were feasible for RV.

With regard to newly described viruses, HBoV was recorded in 13% of cases and HMPV in 5.2%. In our series of CAP-hospitalized children, HBoV was the third most frequently detected virus. This result confirms those of Cilla et al[3] who recently identified HBoV in 14.2% of 315 children aged <3 years with CAP and Honkinen et al[23] who detected HBoV in 18% of 76 children hospitalized with pneumonia. HBoV was first isolated in 2005 in nasopharyngeal aspirate specimens from children with respiratory tract infection.[24] Since then, it has frequently been detected in coinfection with other respiratory viruses and can be identified for prolonged periods.[9,25] Thus, it may be challenging to demonstrate the clinical significance of HBoV detection.[26] However, several studies have shown that detection of HBoV is significantly higher in sick children than in healthy ones.[21,27] Furthermore, there is serological evidence that clearly suggests that HBoV is a cause of human infection.[28]

HMPV, first discovered in the Netherlands in 2001,[29] has been increasingly recognized as a major cause of lower respiratory tract infections in young children worldwide.[30,31] The association of HMPV with acute bronchiolitis has been well documented, as well as its clinical similarities with RSV.[7,31,32] However, the role of HMPV in CAP has been less studied. Our findings confirm that HMPV is also involved in CAP episodes in children (5.2%), although less frequently than RSV, RV, HBoV and adenovirus. Exact numbers of different viruses are difficult to compare from one study to another because several virologic techniques and patient inclusion criteria were applied. Cilla et al[3] found HMPV in 11.5% of children with CAP and Wolf et al[16] in 8.5%; however, only children <3 and 5 years, respectively, were included in these studies. Several reports have suggested that the frequency of HMPV infection is higher in younger children.[31,33] Thus, the short age of patients included might have biased the conclusion.

Multiple viral infections were detected in 30% of patients with positive viral detection and were even more prevalent in younger children (34.5%). This is one of the highest rates of viral coinfection in children with CAP. HBoV was the virus associated with the highest percentage of coinfection (73%), followed by adenovirus (50%) and RV (45%). Similar results were described by Fry et al[34] who found HBoV as coinfection in 83% of 20 outpatients <5 years with pneumonia. The role of dual or multiple viral infections is still unclear and different results regarding its severity can be found in literature.[3,35] The present study does not suggest greater severity in viral coinfections than in single viral infections because, after stratifying by age, only 1 difference could be found between both groups: the shorter duration of oxygen therapy in the confections group. Similar results have been found by our group in hospitalized children with other forms of respiratory infections.[7,35]

On the contrary some differences could be detected between virus-positive and virus-negative CAP patients: hypoxia and wheezing were more frequently present in virus-positive children, who received less antibiotic therapy than virus-negative patients. Curiously enough, virus-positive and virus-negative CAP showed identical monthly distribution and both of them increased in March.

When clinical characteristics associated with the different viruses, as single infections, were compared with those associated with RSV, some significant differences were revealed. HBoV-associated CAP in children >18 months was more likely to be considered a bacterial infection, because they had significantly higher temperature, higher WBC count and higher levels of RCP than RSV patients. For those reasons, they received more frequent antibiotic treatment than RSV children. However, RSV children were younger and needed longer hospital stay.

RV-associated CAP also showed some different clinical characteristics in comparison with RSV. RV patients <18 months were predominantly males and, like HBoV, had a significantly higher WBC count and CRP levels and received more frequent antibiotic treatment than RSV children. Curiously enough, RV was

associated with wheezing and hypoxia less frequently than RSV. These findings confirm our previous results about pediatric RV infection[17]: children hospitalized with RV infections are frequently diagnosed of pneumonia. Moreover, RV-type B is associated with fever, radiographic infiltrates and antibiotic treatment more frequently than other RV types.[17]

HMPV-associated CAP was clinically very similar to the RSV-one. Only 2 differences could be found: the higher rate of intensive care unit admission in HMPV-patients ≥18 months and the younger age in the RSV group. Some studies have suggested more severity of HMPV-associated infections,[36] especially in coinfection with RSV.[37] However, most studies have found no difference in severity between RSV and HMPV infections.[8,38–40]

Recently, interest has grown with respect to the interaction of bacteria and viruses in the pathogenesis of pneumonia. Evidence from cell culture, ecological, postmortem and clinical studies supports this area of interest.[41-43] A feasible hypothesis is that viral infection is followed by secondary bacterial infection. However, currently available procedures for the diagnosis of bacterial respiratory infections in children have a low diagnostic yield, being probably underestimated in many cases. In our study, a blood culture was obtained in 20 of 884 patients, with *S. pneumoniae* being the most frequently identified bacteria. In spite of the limited number, 2 findings deserve to be highlighted: first, our rate of bacterial CAP showed a clear seasonal pattern, increasing in October and decreasing after April as has been described[43]; second, we found one of the highest rates of viral-bacterial coinfection (66.7%) described in literature.[11,12,14,15,23,44] In our series, the most common viruses associated with bacterial infections were RSV, influenza A and RV. Two children with bacterial infection needed intensive care unit admission. Both of them presented viral coinfection. These findings, as others published, suggest that mixed infections could induce a more severe inflammatory and clinical disease than individual bacterial or viral infections.[45] However, the results must be interpreted with caution because probably the true incidence of viral and bacterial coinfection is being underestimated as a result of the above mentioned problems in bacterial diagnosis.

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Current Abstracts

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Transmission of Varicella Zoster Virus From Individuals With Herpes Zoster or Varicella in School and Day-care Settings

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In the first 10 years following the 1996 recommendation of a routine 1-dose varicella vaccination program, there has been a dramatic reduction in varicella-associated morbidity and mortality in the United States. With the implementation of a routine second dose of varicella vaccine, further declines in the incidence of varicella are expected. As the epidemiology of varicella changes, it is likely that exposure to herpes zoster (HZ) cases will play a more prominent role in varicella zoster virus (VZV) transmission and account for an increasing proportion of varicella cases. The authors investigated how HZ contributed to varicella incidence in schools and day-care facilities in Philadelphia by determining the proportions of secondary varicella cases that were associated with exposure to cases of HZ or varicella reported between September 2003 and June 2010. The influence of varicella vaccination status and disease severity on VZV transmission was assessed and potential characteristics of HZ cases that might make transmission of VZV more likely were explored.

This retrospective analysis is based on HZ and varicella surveillance data for cases reported from schools and day-care facilities in Philadelphia during 7 consecutive academic years, defined as the interval from September through June. The study period started with the 2003–2004 academic year, when the Philadelphia Department of Public Health (PDPH) began documenting enforcement of requirements for varicella vaccination among children entering the school system for the first time. Since 1995, both varicella and HZ have been reported in Philadelphia. PDPH has conducted active surveillance for these conditions in West Philadelphia, where approximately one-fifth of the city's 1.4 million reside, and passive surveillance for both in the remainder of the city. Active surveillance is conducted in >300 sites, including 211 schools and day-care facilities, where cases or the absence of cases are reported twice a month. Cases are reported when they occur in the passive surveillance areas.

Mild varicella was defined as the presence of <50 lesions, whereas moderate disease was defined as the presence of ≥50 lesions. A varicella case was considered to be sporadic if it was reported from a school or day-care facility >6 weeks after and ≥10 days before (minimum incubation period) other reports of varicella or HZ from the same facility. A varicella case was considered to be secondary if it occurred between 10 days and 3 weeks after a report of a case of HZ or sporadic varicella from the same institution. An outbreak was defined as the occurrence of ≥5 secondary varicella cases at the same facility within 3 weeks of the HZ or sporadic varicella case that could have been associated with transmission.

During September 2003 to June 2010, PDPH was notified of 2296 cases of HZ and varicella from a school or day-care setting in Philadelphia. Of this total, 1648 cases were HZ or sporadic varicella, including 290 HZ cases (18%) and 1358 sporadic varicella cases (82%). The remaining 648 cases were secondary varicella, of which 499 (77%) had complete information available from detailed or modified case investigations; none reported exposure to VZV outside of the school or day-care setting. A total of 24% of HZ cases and 17% of sporadic varicella cases in school and day-care facilities throughout Philadelphia were reported through active surveillance conducted in West Philadelphia.

Of the 648 secondary varicella cases, 84 (13%) resulted from exposure to 27 HZ cases (9% of the 290 HZ cases) in a facility and 564 (87%) resulted from exposure to 205 sporadic varicella cases (15% of the 1358 sporadic varicella cases) in a facility. Exposure to HZ or sporadic varicella cases resulted in similar proportions of single secondary cases (55% and 56%, respectively) and outbreak-associated cases (14% for both). The remaining secondary cases were in clusters of 2–4 cases. The median numbers of secondary cases among outbreaks associated with exposure to HZ and sporadic varicella cases were 8 and 10, respectively. The proportion of individuals with secondary varicella who had mild disease was similar for those exposed to HZ and varicella (70% and 72%, respectively).

A greater proportion of unvaccinated individuals with sporadic varicella were associated with VZV transmission (29%) compared with the proportion of vaccinated individuals with HZ (8%) or sporadic varicella (18%). The proportion of unvaccinated individuals with HZ who were associated with transmission (23%) was not statistically significantly different from the proportions of vaccinated and unvaccinated individuals with sporadic varicella associated with transmission.

Comment: The results indicate that, in these group settings, VZV transmission from individuals with HZ contributes to varicella morbidity. Ten percent of the total cases reported during the study period were epidemiologically linked to HZ. None of the additional risk factors examined, including age, vaccination status, rash location and rash size, were associated with VZV transmission from an individual with HZ. The finding that rashes on the trunk were just as likely to spread disease as those involving exposed rashes on the arms and legs supports evidence that transmission can occur even when an HZ rash is covered. In addition, stratification by vaccination status suggested that vaccinated individuals with HZ were as likely as vaccinated individuals with varicella to be associated with secondary varicella cases.

As the absolute number of varicella infections continues to decline with universal implementation of a 2-dose varicella vaccine schedule, it is anticipated that HZ will play an increasingly significant role in secondary transmission (Bloch KC and Johnson JG. *J Infect Dis*. 2012;205:1331–1333). Recognition of the importance of HZ in perpetuating VZV infections has significant implications for public health practices in pediatric group settings. Further studies focusing on the HZ infectivity in both the community and hospital are needed to accurately quantify risk and guide prevention strategy.