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Prevalence and Associated Factors with Mixed Coinfections among under 5-Year-Old Children with Severe Viral Pneumonia in Vietnam

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Abstract

Community-acquired pneumonia (CAP) is well-recognized as a leading cause of disease burden in children. This study aimed to identify the prevalence of coinfection and associated factors in Vietnamese children ages 1 month to 5 years with viral pneumonia. We performed a cross-sectional study of children who were diagnosed with severe viral pneumonia. Demographic, clinical, and subclinical characteristics were compared between children with viral alone and bacterial coinfection. Multivariate logistic regression was used to determine which factors were associated with risk of coinfection. Of 202 children with severe viral pneumonia, the most common causative agent was respiratory syncytial virus (respiratory syncytial virus [RSV]: 36.1%), followed by influenza virus A (24.3%) and adenovirus (19.8%). Fifty-three children (26.2%) had bacterial superinfection and/or coinfection with other viruses. *Haemophilus influenza* was the most common bacterium (9.4%), followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (with 4.0%). In infants (toddlers), ages 12 to 24 months with severe viral pneumonia, (odds ratio [OR] = 3.37, 95% confidence interval [CI]: 1.22–9.33), the higher concentrations of procalcitonin (PCT; OR = 1.16; 95% CI: 1.00–1.34), and neutrophils (OR = 1.13; 95% CI: 1.04–1.22) were associated with a higher risk of coinfection. This study underlined the pervasiveness of coinfections among young children with severe viral pneumonia. Provision of effective antiviral treatment, especially for RSV, as well as the advancement of sensitive and rapid diagnostic tools for screening pathogens of pneumonia, is critical to reducing the burden of this disease.

Keywords
- bacterial
- viral
- severe pneumonia
- coinfection

Key Messages

This study underlined the pervasiveness of coinfections among young children with severe viral pneumonia. Provision of effective antiviral treatment, especially for respiratory syncytial virus (RSV), as well as the advancement of sensitive and rapid diagnostic tools for screening pathogens of pneumonia, is critical to reducing the burden of this disease.

Introduction

Globally, community-acquired pneumonia (CAP) has been well-recognized as a leading cause of disease burden in children under 5 years. CAP is responsible for approximately 2 million infant deaths annually.[1,2] However, the management of this disease in the hospital still faces a significant challenge due to critical knowledge gaps about the etiology and clinical manifestations of CAP in young children.[3]

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Viruses have been identified as the most common causes of CAP, with bacterial pneumonia being less common.[1,3,4] Typical viruses include respiratory syncytial virus (RSV),[5] rhinovirus, influenza virus, and adenovirus. However, there are usually no specific clinical symptoms to definitively diagnose the specific type of virus. Moreover, recent advanced molecular techniques confirm the pervasiveness of virus-virus and virus–bacterium coinfections.[6–8] Previous work figured out that approximately 14 to 35% of infants with CAP suffered coinfections.[6–10] Younger age, admission to an intensive care unit, and comorbidity are significant predictors of coinfection conditions.[4,11,12]

In Vietnam, the number of children with pneumonia accounts for 30 to 40% of cases of medical examination and treatment in hospitals.[13] Additionally, 75% of deaths due to respiratory diseases and 30 to 35% of deaths among children.[13] Studies of pneumonia in Vietnamese children have been performed previously[14–16]; however, evidence about coinfections and their risk factors has not been thoroughly investigated. This study aims to identify the prevalence of coinfection and associated factors Vietnamese children under 5 years with viral pneumonia.

Patients and Methods

Study Designs

A cross-sectional study was conducted of 202 children with severe viral pneumonia who treated at the National Hospital of Pediatrics from January 2015 to March 2017,according to World Health Organizations (WHO)-2013 standards.[17] Severe cases of viral pneumonia were defined as follows: (1) having cough or difficulty breathing; (2) finding viruses in nasal fluid, phlegm, or sputum; and at least one of the following main symptoms: (1) cyanosis or SpO_2 <90%, (2) severe respiratory distress (moaning and intercostal muscle external retraction), (3) inability to tolerate enteral fluids, (4) loss of consciousness or coma, and/or (5) convulsions.

We excluded children who (1) age below 1 month or above 5 years; (2) had nonviral pneumonia (for example pneumonia after drowning, chemical pneumonia, aspiration pneumonia); (3) had chronic, associated congenital diseases, or not (e.g., airway malformation, congenital lung disease, liver failure, kidney failure, cystic fibrosis, chronic granulomatous disease, or immune deficiency); or (4) were eligible to participate in the study but the parents or guardian did not agree to participate. This study was approved by the Institutional Review Board of Vietnam Military Medical University (Code: 92/QĐ-HVQY, January 21, 2015).

Data Collection

All participants after hospitalization were carefully examined clinical symptoms by pediatrics. Demographic information and medical history were collected from parents or guardians. The specimens were collected and sent to the laboratory within the first 1 hour, refrigerated, and performed at the Department of Molecular Biology, National Hospital of Pediatrics. Also, participants underwent one laboratory draw for several tests, including complete blood counts, interleukin (IL)-6, high-sensitivity C-reactive protein (hsCRP), and procalcitonin (PCT).

Specimen Collection and Blood Tests

One milliliter of vascular blood was taken into the tube with ethylenediaminetetraacetic (EDTA) upon hospitalization for hematological tests. The tests were run by ABX Micros ES60. Meanwhile, biochemical tests were conducted by taking 2 mL of venous blood when the patient was hospitalized, does not freeze, centrifuge, and is done. Specimens were put into tubes without anticoagulants or with anticoagulants such as Li-Heparin and K3-EDTA. After drawing blood, specimens were centrifuged to extract serum or plasma. The level of hsCRP was determined via turbidity measurement using the Olympus AU 2700 machine. PCT concentration was measured via the luminescent immunization method using the ADVIA Centaur machine of Siemens company. Meanwhile, IL-6 was measured by using BioRad's Bio-Plex Protein Array System.

Viral Detection

Influenza virus A, influenza virus B, and RSV were detected via rapid tests that used the immunochromatographic method. Rhinovirus and adenovirus were identified by utilizing the real-time polymerase chain reaction (RT-PCR). Each patient received 1 mL of blood and 2 mL of nasopharyngeal fluid upon admission. Samples collected were sent to the laboratory within the first hour, refrigerated, and tested. The RT-PCR method was conducted on RT-PCR ABI 7500 and ABI 7500 FAST machines, following the procedure of the Department of Molecular Biology, National Hospital of Pediatrics.

Samples of respiratory fluid collected were used for total RNA/DNA extraction (MagNA Pure LC Total Nucleic acid Isolation Kit, Roche) on MagNA Pure LC 2.0 automatic extraction system (Roche). The forward primers were: GCC ACG GTG GGG TTT CTA AAC TT, the reverse primers were GCC CCA GTG GTC TTA CATGCA CT C, and the probe sequences were carboxyfluorescein (FAM), TGC ACC AGA CCC GGG CTC AGG TAC TCC GA, tetramethyl-6-carboxyrhodamine (TAMRA). Reaction components include: 0.625 µL concentration of 10 pM of each primer; 0.5 µL concentration of 10 pM probe; 12.5 µL 2X PCR master mix (Qiagen); 5 µL DNA and H_2O, which were added in total reaction of 25 µL. Reaction program included: 500—2 minutes, 950—15 minutes, and 45 cycles of 950—15 seconds, and 580—1 minute. RT-PCR assays for Adenovirus detection used oligonucleotide primers and dual-labeled hydrolysis probes (Taqman). The estimated time for running samples was approximately 125 minutes. The positive control was from the plasmid of Gothenburg University, Sweden, and the negative control was the water component in the PCR reaction mixture. Results were read and analyzed using a RT ABI 7500 Fast system.

Bacterial Detection

Bacterial testing was performed by the Vitek-2 machine. The bacterium was detected by using the colorimetric method to identify the chemical, biological properties of each bacteria via color change of environmental wells in the card. Moreover, an antibiotic method was also utilized by using the minimum inhibitory concentration measurement method,

which measured turbidity to monitor the development of microorganisms in the card wells. These two methods were performed according to the principle of light intensity reduction. The system used wavelength 660, 568, and 428.

Statistical Analysis

Chi-squared and Kruskal–Wallis tests were utilized to compare demographic, clinical, and paraclinical characteristics between children with pneumonia caused by one virus only versus those in which more than one virus was identified (viral coinfection) and versus those in which bacterial superinfection occurred. STATA software 15.0 was used to analyze data. Multivariate logistic regression was performed to identify the associated factors with mixed coinfections. A stepwise backward selection strategy was used, using the *p*-value of a log-likelihood test of less than 0.2 as a threshold to select variables. A two-tailed *p*-value of less than 0.05 was considered statistically significant.

Results

Of 202 children with severe viral pneumonia, overall, the mean age of patients was 8.6 months (standard deviation [SD] = 9.6, range: 1.0–48.7 months). Among them, 59.9% of study participants were male. Also, there was 19.8% of children were born with low birth weight, 19.8% were born premature, 52% suffered from malnutrition, and 25.7% were not fully. ►**Table 1** shows that the majority of patients had RSV (36.1%), followed by influenza virus A (24.3%) and adenovirus (19.8%). There were 53 children (26.2%) coinfected with bacteria or/and other viruses.

►**Table 2** illustrated that among children with bacteria superinfection, the incidence of *Haemophilus influenza* was the highest (45.2%), followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (with 19.1%).

The distribution of coinfection status, according to sociodemographic characteristics, is depicted in ►**Table 3**. No difference was found among these coinfection conditions regarding age, gender, new-born weight, nutritional status, and immunization status ($p > 0.05$).

Clinical characteristics of different coinfection conditions are shown in ►**Table 4**. Fever, cyanosis, and not hepatosplenomegaly were significantly different across groups ($p < 0.05$).

Table 2 Type of bacterium among viral pneumonia children with coinfections

Type of bacterium	*n*	Children with bacterial coinfections (%)	Percentage in entire sample
Haemophilus influenza	19	45.2	9.4
Klebsiella pneumoniae	8	19.1	4.0
Pseudomonas aeruginosa	8	19.1	4.0
Streptococcus pneumoniae	7	16.7	3.5
Acinetobacter baumannii	4	9.5	2.0
Burkholderia cepacia	1	2.4	0.5
Staphylococcus aureus	1	2.4	0.5

The total white blood cell count, neutrophils cell count, concentration of hsCRP, and PCT were significantly higher in patients with bacterial coinfections or bacterial and viral coinfections ($p < 0.05$).Invasive mechanical ventilation was significantly pervasive in infants with both bacterial and viral coinfections ($p < 0.05$). They also had a significantly higher length of stay compared with other groups ($p < 0.05$).

The multivariate regression model showed that in toddlers ages12 to 24 months with severe viral pneumonia (odds ratio [OR] = 3.37, 95% confidence interval [CI]: 1.22–9.33), the higher concentration level of PCT (OR = 1.16; 95% CI: 1.00–1.34), and neutrophils (OR = 1.13; 95% CI: 1.04–1.22) were associated with a higher risk of suffering from any type of coinfection (►**Table 5**).

Discussion

This study contributes to global literature regarding the etiology and clinical characteristics of severe viral pneumonia among infants in Vietnam. Results indicated that RSV and influenza virus A was the most common viral pathogens, and one-fifth of patients identified coinfections. Age and level of PCT and Neutrophils were important markers to predict coinfection conditions.

The pattern of viral pathogens in the current study differs from other previous studies. In Pakistan, a study of 817 infants and children under 2 years of age showed that the prevalence

Table 1 Etiology of viral pneumonia

Characteristics	Single virus (*n* = 149)	Coinfection with bacteria (*n* = 34)	Coinfection with virus (*n* = 11)	Coinfection with bacteria and virus (*n* = 8)	Total (*n* = 202)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Influenza virus A	36 (73.5)	5 (10.2)	6 (12.2)	2 (4.1)	49 (24.3)
Influenza virus B	10 (71.4)	4 (28.6)	0 (0.0)	0 (0.0)	14 (6.9)
RSV	59 (80.8)	11 (15.1)	2 (2.7)	1 (1.4)	73 (36.1)
Adenovirus	28 (70.0)	7 (17.5)	3 (7.5)	2 (5.0)	40 (19.8)
Rhinovirus	16 (61.5)	7 (26.9)	0 (0.0)	3 (11.5)	26 (12.9)

Abbreviation: RSV, respiratory syncytial virus.

Table 3 Patients' characteristics according to coinfection status

Characteristics	Single virus ($n = 149$)	Coinfection with bacteria ($n = 34$)	Coinfection with virus ($n = 11$)	Coinfection with bacteria and virus ($n = 8$)	*p*-Value
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Age group (mo)					
0–6	88 (76.5)	16 (13.9)	6 (5.2)	5 (4.4)	0.19
> 6–12	31 (77.5)	8 (20.0)	0 (0.0)	1 (2.5)	
> 12–24	14 (51.9)	8 (29.6)	3 (11.1)	2 (7.4)	
> 24	16 (80.0)	2 (10.0)	2 (10.0)	0 (0.0)	
Gender					
Female	63 (77.8)	13 (16.1)	2 (2.5)	3 (3.7)	0.46
Male	86 (71.1)	21 (17.4)	9 (7.4)	5 (4.1)	
Birth weight (g)					
< 2,500	26 (65.0)	9 (22.5)	2 (5.0)	3 (7.5)	0.38
≥ 2,500	123 (75.9)	25 (15.4)	9 (5.6)	5 (3.1)	
Nutritional status					
Normal	51 (75.0)	11 (16.2)	5 (7.4)	1 (1.5)	0.65
Malnutrition	75 (71.4)	18 (17.1)	6 (5.7)	6 (5.7)	
Overweight/obesity	23 (79.3)	5 (17.2)	0 (0.0)	1 (3.5)	
Immunization					
Full	114 (76.0)	26 (17.3)	7 (4.7)	3 (2.0)	0.08
Missing	35 (67.3)	8 (15.4)	4 (7.7)	5 (9.6)	

of enterovirus/rhinovirus infection was 51.7%, followed by influenza viruses (8.3%) and RSV (5.7%).[18] A study in China showed that the most common causative viruses were enterovirus/rhinovirus (54.1) %), RSV (51.1%), Human bocavirus (33.8%), parainfluenza viruses type 3 (PIV3; 15.4%), and adenovirus (ADV; 13.0%).[19] Another study in China indicated a similar finding with our study that RSV was the most common pathogen,[4] which was consistent with other studies in the United States of America[7] and Spain.[20]

Coinfection was common among children with severe viral pneumonia in our study, approximately 25.3% of our patients experienced coinfection in any type. This rate was a slightly lower than that reported in previous studies in China and the United States, which found that 34.6% of infants with CAP suffering from coinfections,[4,21] but was similar to another nationally representative study in the United States, which indicated that 26% had coinfections.[7] Pavia et al found that among 58 pediatric patients with pneumonia, 35% were coinfected.[22] Nascimento-Carvalho et al in a group of 25 pneumonia children with pleural effusion, showed that 22% of cases had viral–bacterial coinfections.[23] Juvén et al indicated that approximately 30% of cases suffered from viral–bacterial coinfections.[24] Moreover, the study results showed that the incidence of *H. influenza* was the highest (9.4% of the entire sample), followed by *K. pneumoniae* and *P. aeruginosa* (with 4.0% of the entire sample). *Streptococcus pneumoniae* had been found in 3.5% of the sample, which was consistent with prior studies in China (3.0%) and the United States (4%).[4,7] However, 9.4% of our study population were infected with another virus, which was much lower compared with the previous study in the United States (26.0%).[7] The disparities might be attributable to the seasonal or geographical factors.

The results of this study showed that the majority of clinical characteristics could not distinguish between coinfection groups except fever, cyanosis, hepatosplenomegaly, and invasive mechanical ventilation. Similarly, analysis of paraclinical indicators indicated that the total white blood cell count, neutrophils cell count, concentration of hsCRP, and PCT were significantly higher among infants with bacterial superinfection versus single virus. This result was in line with prior study in the United States, which revealed that the prevalence of fever, as well as the level of neutrophils, were the lowest among patients having viral infections only or viral coinfections.[21] Similarly, the study in China found that infants with mixed infections had a higher rate of fever than that of patients who were infected with a single virus.[4] We conjecture that pediatric patients having viral coinfections presented a higher level of inflammation than those having an only single viral infection.[4] Additionally, the regression model confirmed the associations between PCT and neutrophils with mixed coinfections after adjusting to other covariates, suggesting potential biomarkers to predict coinfections among young children with severe viral pneumonia.

Limitations

This study had several limitations. The study was conducted at the hospital; therefore, the results of the study were only

Table 4 Clinical characteristics regarding coinfection status

Characteristics	Single virus ($n = 149$)	Coinfection with bacteria ($n = 34$)	Coinfection with virus ($n = 11$)	Coinfection with bacteria and virus ($n = 8$)	*p*-Value
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Fever	100 (67.1)	30 (88.2)	10 (90.9)	6 (75.0)	0.04
Rapid heart pulse	80 (53.7)	20 (58.8)	10 (90.9)	4 (50.0)	0.11
Runny nose	61 (40.9)	14 (41.2)	4 (36.4)	1 (12.5)	0.45
Wheezing	125 (83.9)	29 (85.3)	9 (81.8)	6 (75.0)	0.91
Grunting	9 (6.0)	1 (2.9)	2 (18.2)	2 (25.0)	0.07
Poor feeding	117 (78.5)	23 (67.7)	10 (90.9)	8 (100.0)	0.14
Excessive crying	36 (24.2)	11 (32.4)	1 (9.1)	4 (50.0)	0.17
Convulsions	9 (6.0)	0 (0.0)	1 (9.1)	1 (12.5)	0.37
Cyanosis	35 (23.5)	7 (20.6)	5 (45.5)	8 (100.0)	<0.01
Diarrhea	44 (29.5)	11 (32.4)	1 (9.1)	1 (12.5)	0.34
No hepatosplenomegaly	138 (92.6)	30 (88.2)	8 (72.7)	5 (62.5)	0.01
Invasive mechanical ventilation	11 (7.4)	7 (21.2)	2 (18.2)	5 (62.5)	<0.01
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Time from illness onset to admission (d)	7.2 (6.6)	5.9 (4.8)	5.5 (3.9)	7.6 (5.2)	0.93
Length of stay (d)	13.2 (13.6)	23.4 (33.1)	17.4 (14.5)	33.5 (22.3)	<0.01
Hemoglobin (g/dL)	105.2 (14.3)	105.2 (13.4)	105.5 (8.5)	94.6 (9.6)	0.13
White blood cell (G/L)	11.1 (5.1)	14.8 (7.7)	9.1 (2.8)	14.4 (6.2)	<0.01
Neutrophils (G/L)	4.7 (3.6)	8.3 (6.4)	4.1 (1.8)	7.9 (5.2)	<0.01
Lymph (G/L)	4.7 (2.6)	4.6 (2.4)	3.3 (1.2)	5.1 (2.5)	0.30
Mono (G/L)	1.3 (1.1)	1.5 (1.0)	1.2 (0.7)	1.3 (0.6)	0.72
Platelet (G/L)	382.6 (155.6)	417.7 (230.1)	324.7 (163.8)	437.1 (190.9)	0.42
hsCRP (mg/dL)	12.7 (25.6)	32.5 (51.8)	8.1 (10.8)	9.3 (10.6)	0.02
PCT (ng/mL)	1.1 (1.7)	3.4 (5.9)	0.8 (1.1)	6.8 (15.1)	<0.01
IL-6 (pg/mL)	26.0 (82.1)	22.1 (36.9)	13.8 (12.4)	98.9 (171.1)	0.13

Abbreviations: hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; SD, standard deviation.

Table 5 Associated factors with mixed coinfections

Factor	Mixed coinfection (yes/no)			
	OR	*p*	95%CI	
Age group (mo)				
0–6	REF			
> 6–12	0.90	0.84	0.32	2.49
> 12–24	3.37	0.02	1.22	9.33
> 24	1.02	0.97	0.27	3.83
Immunization				
Full injection	REF			
Missing injection	2.02	0.11	0.86	4.73
Cyanosis				
No	REF			
Yes	2.08	0.07	0.93	4.63
No hepatosplenomegaly				
No	REF			
Yes	0.38	0.06	0.14	1.06
PCT (ng/mL)	1.16	0.045	1.00	1.34
Neutrophil (G/L)	1.13	< 0.01	1.04	1.22

Abbreviation: CI, confidence interval; OR, odds ratio; PCT, procalcitonin; REF, reference.

conclusive for the pneumonia children treated at the National Hospital of Pediatrics, and we could not extrapolate to the community. Our sample size was small and conveniently recruited, which thus might reduce our generalizability. Moreover, data on several variables in the study, such as nutritional status and premature birth, were significantly high or not allowed to categorize into more details. The cross-sectional design is a limitation because of its limitations due to its nature.

Conclusion

To conclude, this study underlined the pervasiveness of coinfections among infants and young children with severe viral pneumonia. Provision of effective antiviral treatment, especially for RSV, as well as the advancement of sensitive and rapid diagnostic tools for screening pathogens of pneumonia, is critical to reducing the burden of this disease.

Conflicts of Interest
None declared.

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