Arch Pediatr Infect Dis. ; In Press(In Press): e159918 https://doi.org/10.5812/apid-159918

Published Online: 2025 June 30 **Research Article**

Detection of Non-typeable *Haemophilus influenzae* as a Causative Pathogen of Community-Acquired Pneumonia in Vietnamese Children

Khai Quang Tran [1], Trung Quoc Ly [2], Thu Thi Kim Le [1], Long Duy Phun [1], Tuyen Nguyen Kim Pham [1], Quan Minh Pham [1,*]

[1] Department of Pediatrics, Faculty of Medicine, Can Tho University of Medicine and Pharmacy, Can Tho City 900000, Vietnam
[2] Soctrang Hospital for Women and Children, Soc Trang 950000, Vietnam

[*] ***Corresponding Author:*** Department of Pediatrics, Faculty of Medicine, Can Tho University of Medicine and Pharmacy, Can Tho City 900000, Vietnam. Email: pmquan@ctump.edu.vn

Received: 4 February, 2025; **Revised:** 7 June, 2025; **Accepted:** 24 June, 2025

Abstract

Background: The prevalence of invasive *Haemophilus influenzae* type b (Hib) disease—especially community-acquired pneumonia (CAP)—has significantly decreased due to the widespread use of Hib conjugate vaccines. Non-typeable *H. influenzae* (NTHi) has since emerged as the predominant etiological agent of infections across various age groups in many countries, drawing increasing attention.

Objectives: This study aimed to determine the prevalence of NTHi infection in children with CAP and to compare the clinical and laboratory characteristics of children with NTHi-associated versus other agent-associated CAP.

Methods: This cross-sectional study included 336 children with CAP admitted to Can Tho Children's Hospital, Vietnam, between June 2020 and June 2022. Consecutive eligible patients were enrolled to minimize selection bias. Nasotracheal aspiration samples were collected and analyzed using real-time polymerase chain reaction (PCR) to detect the presence of 70 microbial agents.

Results: No cases of Hib infection were identified. The NTHi was the second most common bacterial agent causing childhood CAP, with a prevalence of 22.9%. Most cases (96.1%) involved co-infections, primarily bacterial (44.2%). The most common co-infection with NTHi was *Streptococcus pneumoniae* (56/77; 72.7%); only 3 of 77 children (3.9%) had CAP due to NTHi alone. Compared to those with other agent-associated CAP, children with NTHi-associated CAP experienced less tachypnea (81.8% vs. 90.3%) and more diarrhea (20.8% vs. 12.4%), along with higher white blood cell (WBC) counts (median: 15.1 G/L vs. 13.4 G/L) and C-reactive protein (CRP) levels (median: 14.9 mg/L vs. 11.0 mg/L) ($P < 0.05$). In multivariate logistic regression analysis, only two factors were independently associated with NTHi-associated CAP: reduced tachypnea (OR = 2.21; 95% CI: 1.07 - 4.59) and elevated WBC count (OR = 1.05; 95% CI: 1.00 - 1.10).

Conclusions: The NTHi has replaced Hib as a leading cause of CAP in children. Patients presenting with less tachypnea and elevated WBC counts are more likely to have NTHi-associated CAP.

Keywords: Non-typeable *Haemophilus influenzae*, Vietnamese, Children

1. Background

Pneumonia remains a major cause of mortality among children under five years of age, particularly in low- and middle-income countries. The World Health Organization (WHO) estimates that approximately 2,000,000 children under five die each year from community-acquired pneumonia (CAP), with the majority of deaths occurring in developing countries (1, 2). According to previous studies, *Streptococcus pneumoniae* (pneumococcus) is responsible for 30% to 50% of pneumonia cases (3-5), while *Haemophilus influenzae* accounts for 10% to 30% (6). However, the role of non-typeable *H. influenzae* (NTHi) remains relatively underrecognized and is still considered controversial (2).

How to Cite: Tran K Q, Ly T Q, Le T T K, Phun L D, Pham T N K, et al. Detection of Non-typeable *Haemophilus influenzae* as a Causative Pathogen of Community-Acquired Pneumonia in Vietnamese Children. Arch Pediatr Infect Dis. 2025; In Press (In Press): e159918. https://doi.org/10.5812/apid-159918.

Between 2003 and 2012, the annual incidence of invasive NTHi disease was reported to be 1.6 cases per 100,000 children under five years old (2). With the global expansion of pneumococcal and Hib vaccination programs, infection patterns have shifted—particularly for Hib, which induces immunity even after a single vaccine dose (7). As a result, Hib is no longer a predominant pathogen, whereas NTHi is gradually becoming more prevalent (8). Recent studies on CAP in children have reported NTHi detection rates ranging from 4% to 26% (9). While NTHi is a well-established cause of pneumonia in adults, its role in pediatric pneumonia remains unclear and is still under debate, particularly in Vietnam (10).

2. Objectives

This study aimed to evaluate the frequency of NTHi as a causative agent in pediatric CAP and to compare the clinical and laboratory characteristics of children with NTHi-associated CAP versus those with CAP caused by other pathogens.

3. Methods

3.1. Study Design and Data Collection

This cross-sectional study investigated 336 children with community-acquired pneumonia (CAP), admitted to Can Tho Children's Hospital—the largest pediatric healthcare center in the Mekong Delta region of southern Vietnam—between June 2020 and June 2022.

The study included children aged between two months and fifteen years who were hospitalized with CAP and met the inclusion criteria. Pneumonia was clinically diagnosed based on WHO guidelines, which require symptoms such as cough or difficulty in breathing, along with at least one of the following clinical signs: Tachypnea, chest wall retraction, or abnormal lung sounds such as hypoventilation or rales (11). All patients were enrolled within 48 hours of hospital admission and had radiographically confirmed pneumonia. Exclusion criteria included hospitalization within the previous 30 days, aspiration pneumonia, or a history of drowning. Nasotracheal aspiration (NTA) samples containing more than 10 squamous epithelial cells and fewer than 25 polymorphonuclear cells per low-power field (100X) were considered of low quality and excluded (2).

The minimum required sample size was calculated using the formula:

$$n = \frac{Z^2 \times P \times (1 - P)}{d^2} \quad (1)$$

where n = sample size, Z = 1.96 for 95% confidence level, P = estimated prevalence of *H. influenzae* (0.37), and d = margin of error (0.06). These parameters were based on data from Yoshida et al.'s 2010 study in Central Vietnam (12), yielding a minimum sample size of 249. To ensure adequate power and reduce selection bias, 336 consecutive eligible patients were enrolled.

The NTA was performed using a Mucus Extractor (Global Medikit Limited, New Delhi, India). Specimens were transported within 48 hours to the Vietnam Research and Development Institute of Clinical Microbiology in Ho Chi Minh City, which is certified under ISO 9001:2015, ISO 13485:2017, and WHO-GMP standards. Eight low-quality samples were excluded.

The real-time polymerase chain reaction (PCR) procedure for detecting microbiological agents involved the following steps: (1) Samples were blended with phosphate-buffered saline supplemented with N-acetyl L-cysteine; (2) nucleic acid extraction was performed using the BIO-RAD CFX96 automated system (Hercules, California, USA) (13); (3) extracted nucleic acids were subjected to real-time PCR using specific primers and TaqMan Probes (Thermo Fisher Scientific) along with the NKRNADNAprep-MAGBEAD reagent kit (Nam Khoa Company, Vietnam) to detect and quantify 70 microbial agents (Appendix 1); a PCR result was considered positive when a single pathogen was identified in quantities greater than 10^5 copies/mL, a threshold previously associated with infection (14).

Demographic data—including age, sex, Hib vaccination status, pneumonia history, and nutritional status—were collected for all eligible patients. Clinical signs and laboratory data, including white blood cell (WBC) count, platelet count, and C-reactive protein (CRP) levels, were compared between children with NTHi-associated CAP and those with CAP due to other pathogens. The highest paraclinical values recorded during hospitalization were used in the analysis.

3.2. Statistical Analysis

Data were analyzed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Quantitative variables were presented as mean ± standard deviation (SD) or as median and interquartile range (IQR) for non-normally distributed data. Qualitative variables were summarized as frequencies and percentages. The chi-square test was used for categorical variables, while independent *t*-tests or the Mann-Whitney U test were

used for continuous variables, depending on data distribution.

A P-value of < 0.05 was considered statistically significant. Multivariate logistic regression was employed to identify independent predictors of NTHi-associated CAP. Variables with a P-value < 0.1 in univariate analysis were included in the multivariate model. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported, and statistical significance was defined as $P < 0.05$.

3.3. Ethical Approval

This study was conducted in accordance with ethical standards emphasizing human dignity, fairness, and welfare. Ethical approval was granted by the Ethics Committee for Biomedical Research at Can Tho University of Medicine and Pharmacy (Can Tho City, Vietnam), under approval number 208/PCT-HĐĐĐ.

4. Results

Between June 2020 and June 2022, nasotracheal aspiration (NTA) samples were collected from 344 pediatric patients diagnosed with community-acquired pneumonia (CAP) and admitted to Can Tho Children's Hospital. Of these, 336 samples met the lower respiratory tract quality criteria, while 8 were excluded due to low quality (>10 squamous epithelial cells or < 25 polymorphonuclear cells per low-power field).

Real-time PCR successfully detected pathogens in 312 out of 336 cases (92.9%). *Haemophilus influenzae* (all non-typeable strains, NTHi) was identified as the second most common bacterial cause of childhood CAP, with a frequency of 77/336 (22.9%), following *S. pneumoniae* at 222/336 (66.1%) (Figure 1).

Enrollment and sample exclusion: Among 344 NTA samples collected, 8 were excluded due to poor quality. The remaining 336 samples were analyzed using real-time PCR.

4.1. Pathogen Detection

Streptococcus pneumoniae (66.1%, 222/336) and non-typeable *H. influenzae* (NTHi; 22.9%, 77/336) were the most prevalent bacterial agents. All *H. influenzae* isolates were non-typeable. Details of co-infections are shown in Figure 2.

The children with CAP had a median age of 17 months. The majority were under two years old (214 cases, 63.7%), followed by those aged two to five years (102 cases, 30.4%), and only 20 children (5.9%) were older than five. The illness was more common in boys (66.7%) than girls (33.3%), with a male-to-female ratio of 2: 1. Hib conjugate vaccination had been administered to 282 of 336 children (83.9%). A total of 69.3% of children had no previous history of pneumonia, while 30.7% had experienced at least one prior episode. Children with acute malnutrition represented a significant proportion (41.7%) (Table 1).

Among the 77 children diagnosed with NTHi-associated CAP, most had co-infections with other pathogens (96.1%). The most common type was bacterial co-infection (44.1%), followed by viral-bacterial co-infection (39.0%). Only 3 out of 77 children (3.9%) had a single NTHi infection (Table 2).

The most frequent co-infecting agents with NTHi were *S. pneumoniae* (56/77, 72.7%), followed by respiratory syncytial virus (RSV) (17/77, 22.1%), Bocavirus (16/77, 20.8%), and *Moraxella catarrhalis* (12/77, 15.6%) (Figure 2).

Clinically, children with NTHi-associated CAP experienced less tachypnea (81.8% vs. 90.3%) and more frequent diarrhea (20.8% vs. 12.4%) compared to those with CAP caused by other agents. They also had significantly higher white blood cell (WBC) counts (median: 15.1 G/L vs. 13.4 G/L) and C-reactive protein (CRP) levels (median: 14.9 mg/L vs. 11.0 mg/L) ($P < 0.05$) (Table 3).

In multivariate logistic regression analysis, only two independent factors were significantly associated with NTHi-associated CAP: reduced tachypnea (OR = 2.21; 95% CI: 1.07 - 4.59) and elevated WBC count (OR = 1.05; 95% CI: 1.00 - 1.10) (Table 4).

5. Discussion

Between June 2020 and June 2022, 344 nasotracheal aspiration (NTA) samples were collected from pediatric CAP patients at Can Tho Children's Hospital. Of these, 336 passed quality control and were included in the analysis. Most patients (63.7%) were under two years of age—considered the most vulnerable group to CAP globally (15, 16). Real-time PCR detected respiratory pathogens in 92.9% (312/336) of the samples, demonstrating superior sensitivity compared to traditional cultures. Non-typeable *H. influenzae* was identified as the second most common pathogen (22.9%, 77/336), following *S. pneumoniae* (66.1%, 222/336).

According to Global Burden of Disease (GBD) models, bacterial infections—especially *S. pneumoniae* and *H. influenzae* type b (Hib)—account for approximately 64% of pneumonia-related deaths in children under five (17). A study from Israel reported that 25% of NTHi infections presented as pneumonia (3). Since 1998, the WHO has recommended the global implementation of Hib conjugate vaccination (18). Following widespread use,

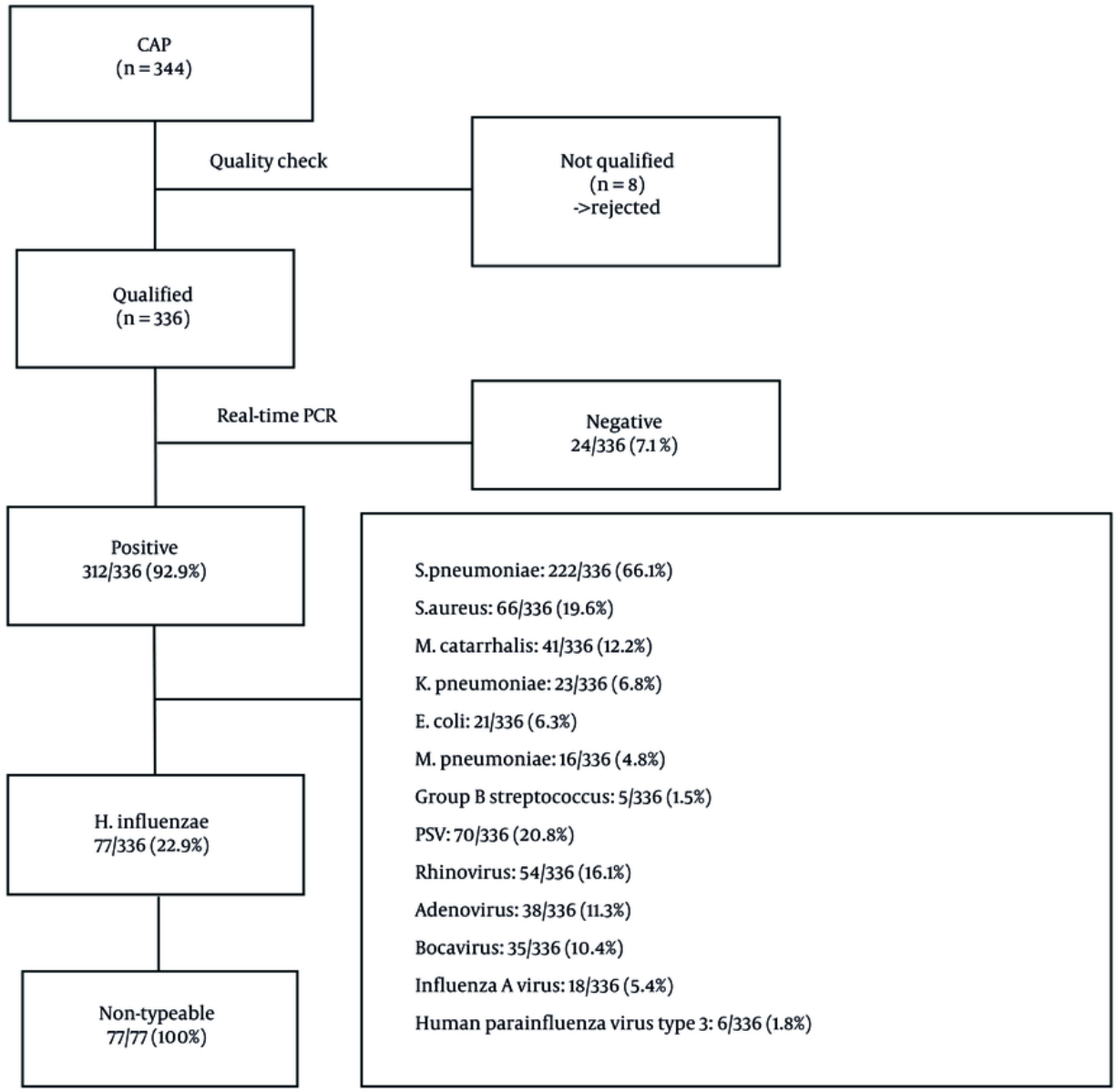

Figure 1. Study flowchart and pathogen distribution in pediatric community-acquired pneumonia cases (abbreviations: CAP, community-acquired pneumonia; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; MRSA, methicillin-resistant *Staphylococcus aureus*).

pathogen trends have shifted, particularly with Hib, due to its ability to induce immunity even after a single vaccine dose (19, 20). As a result, Hib infections have declined, while NTHi has become increasingly recognized as a significant pathogen. Recent studies suggest the 10-valent pneumococcal vaccine may offer partial protection against NTHi, although definitive evidence is still lacking (6, 21). This potential has laid the groundwork for future vaccine development.

In Vietnam, the Hib vaccine was introduced into the national immunization program in 2010, while the pneumococcal vaccine remains a service-based option. In our study, 83.9% of children had received the Hib

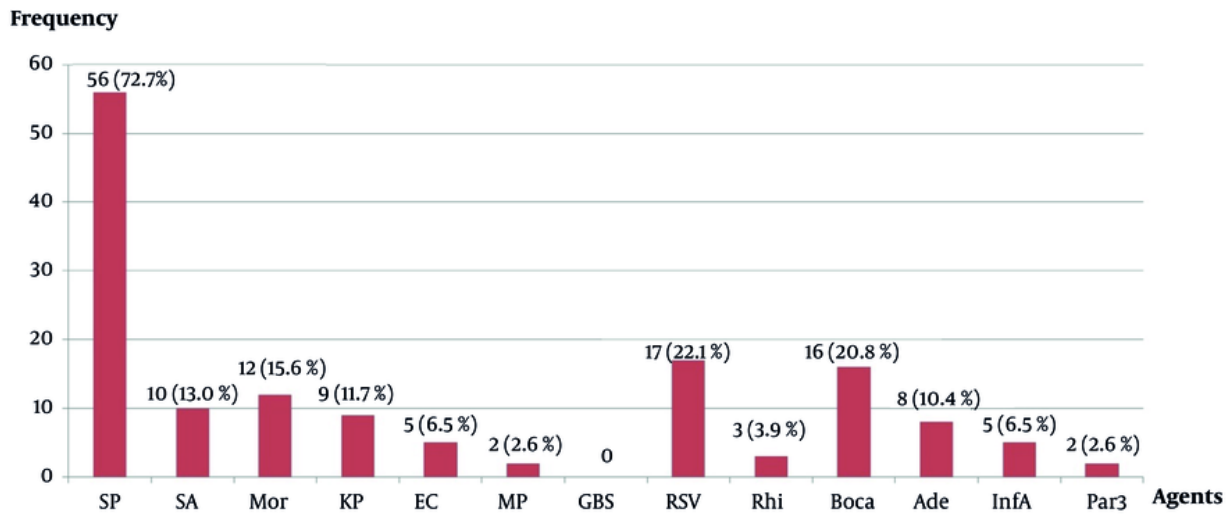

Figure 2. Non-typeable *Haemophilus influenzae* co-infection with other agents (n = 77) (abbreviations: SP, *Streptococcus pneumoniae*; SA, *Staphylococcus aureus*; Mor, *Moraxella catarrhalis*; KP, *Klebsiella pneumoniae*; EC, *Escherichia coli*; MP, *Mycoplasma pneumoniae*; GBS, Group B *Streptococcus*; RSV, respiratory syncytial virus; Rhi, rhinovirus; Boca, bocavirus; Ade, adenovirus; InfA, influenza A virus; Par3, human parainfluenza virus type 3).

vaccine, correlating with the prominence of S. pneumoniae and NTHi as the leading causative agents.

Microbiological co-infection has gained increasing attention in recent years (5, 22, 23). In this study, 96.1% of NTHi-associated CAP cases involved co-infections, primarily bacterial (44.1%), followed by viral-bacterial combinations (39.0%). Non-typeable *H. influenzae* was most commonly co-infected with *S. pneumoniae* (72.7%), aligning with existing literature that identifies these pathogens as the primary CAP agents (24). Due to the high effectiveness of the Hib vaccine, NTHi now predominates in H. influenzae co-infections (25). Respiratory syncytial virus was the most common viral co-infecting agent (22.1%), consistent with prior findings (4). Notably, only 3.9% (3/77) of children had a single NTHi infection.

The NTHi infections are more commonly seen in children with underlying conditions such as immunodeficiency or chronic respiratory disease and are rarely reported in otherwise healthy individuals (19). A study from Germany described by Falade et al. found that 62% of NTHi infections were non-acquired (7). In another study which analyzed 250 children with recurrent or unresponsive pneumonia, up to 51% were associated with NTHi (1). An Australian study identified nearly 20 different genotypes of NTHi, reflecting its considerable strain diversity (21).

Although generally less invasive than Hib, some NTHi strains can cause serious illness in neonates and children with comorbidities (6). In this study, children with NTHi-associated CAP had significantly less tachypnea compared to those with other CAP pathogens (81.8% vs. 90.3%, P = 0.004). Recent studies indicate that childhood pneumonia often lacks distinctive physical signs (26). In Vietnam, pneumonia most consistently presents with fever and cough (100%). The NTHi infections were associated with a higher rate of diarrhea (20.8%, P = 0.001). Laboratory markers such as white blood cell (WBC) count and C-reactive protein (CRP) levels are widely used to predict severity and distinguish bacterial from viral infections (27, 28). In our cohort, NTHi-associated CAP was associated with elevated WBC and CRP values compared to other causes.

Multivariate logistic regression identified two independent factors significantly associated with NTHi-related CAP: Reduced tachypnea (adjusted OR = 2.21; 95% CI: 1.07 - 4.59) and elevated WBC count (adjusted OR = 1.05; 95% CI: 1.00 - 1.10), supporting the bacterial etiology and frequent co-infection profile of NTHi.

One limitation of this study is that data were collected from a single center—Can Tho Children's Hospital—which may limit the generalizability of the findings to other regions with different pathogen distributions and vaccine coverage. Additionally, the

Table 1. Demographic Characteristics of the Patients (n=336) [a]

Variables	Values
Age (y)	
Median, IQR (months)	17 (10 - 30)
< 2	214 (63.7)
2 - 5	102 (30.4)
> 5	20 (5.9)
Sex	
Male	224 (66.7)
Female	112 (33.3)
Hib conjugate vaccination	
Available	282 (83.9)
Not available	18 (5.4)
Not clear	36 (10.7)
History of pneumonia	
Never	233 (69.3)
Once	47 (14.0)
More than once	56 (16.7)
Nutritional status	
Obesity	21 (6.3)
Overweight	51 (15.1)
Normal nutrition	124 (36.9)
Acute malnutrition	140 (41.7)

[z] Abbreviation: Hib, *Haemophilus influenzae* type b

[a] Values are expressed as No. (%) unless otherwise indicated.

Table 2. Distribution of Non-typeable *Haemophilus influenzae* Infection According to Co-infection – Single Infection (n = 77) [a]

Variables	Values	Cumulative Percentage (%)
Bacterial co-infection	34 (44.1)	44.1
Viral-Bacterial co-infection	30 (39.0)	83.1
Viral co-infection	10 (13.0)	96.1
Single infection	3 (3.9)	100

[a] Values are expressed as No. (%) unless otherwise indicated.

clinical impact of co-infections was not analyzed in detail and will be the subject of future investigations.

5.1. Conclusions

The NTHi has replaced Hib as a leading cause of CAP in children. Clinical features such as reduced tachypnea and elevated WBC counts should prompt consideration of NTHi-associated CAP.

Acknowledgements

We would like to thank Can Tho University of Medicine and Pharmacy, Can Tho Children's Hospital, and the Vietnam Research and Development Institute of Clinical Microbiology, Ho Chi Minh City, for their support. We are also grateful to the patients and their families for their participation in this study.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Table 3. Characteristics of Non-typeable *Haemophilus influenzae*-Associated CAP (n=77) and Other Agent-Associated CAP (n=259) [a]

Variables	NTHi-associated CAP (n = 77)	Other agent-associated CAP (n = 259)	P-Value
Symptoms and signs			
Fever	77 (100)	259 (100)	NA
Cough	77 (100)	259 (100)	NA
Vomiting	7 (9.1)	24 (13.9)	0.267
Diarrhoea	16 (20.8)	32 (12.4)	0.001 [b]
Tachypnea	63 (81.8)	234 (90.3)	0.004 [b]
Chest indrawing	40 (51.9)	155 (59.8)	0.218
Accessory muscle used	25 (32.5)	83 (32.0)	0.945
Crackles	68 (88.3)	235 (90.7)	0.531
Wheezing	42 (54.5)	151 (58.3)	0.558
SpO2 ≤ 90%	25 (32.5)	83 (32.0)	0.945
WBC count (G/L)	15.1 (10.8 - 19.3)	13.4 (9.0 - 17.6)	0.017 [c]
Platelet count (G/L)	372.6 ± 119.1	362.1 ± 127.6	0.763
CRP (mg/L)	14.9 (7.6 - 45.3)	11.0 (3.4 - 29.7)	0.007 [c]

[z] Abbreviations: WBC, white blood cell; CRP, C-reactive protein; NA: not applicable.

[a] Values are expressed as mean ± SD or No. (%) unless otherwise indicated.

[b] Significant difference using the chi-square statistical test.

[c] Significant difference using the Mann-Whitney test.

Table 4. Multivariate logistic regression analysis of factors associated with Non-typeable *Haemophilus influenzae*-associated CAP (n = 336)

Variables	Odds Ratio (OR)	95% Confidence Interval (CI)	P-Value
Diarrhoea	0.55	0.27 - 1.13	0.11
Tachypnea	2.21	1.07 - 4.59	0.033
WBC count (G/L)	1.05	1.00 - 1.10	0.042
CRP (mg/L)	1.00	0.99 - 1.01	0.61

Footnotes

Authors' Contribution: Study concept and design: K. Q. T., and Q. M. P; analysis and interpretation of data: T. T. K. L., and K. Q. T.; drafting of the manuscript: L. D. P., T. Q. L.; critical revision of the manuscript for important intellectual content: Q. M. P., and T. N. K. P.; statistical analysis: T. Q. L, and K. Q. T.

Conflict of Interests Statement: The authors declare no conflict of interests.

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: The research complied with ethical standards prioritizing human dignity, fairness, and welfare. Ethical approval for the study was granted by the Ethics Committee for Biomedical Research at Can Tho University of Medicine and Pharmacy (located in Can Tho City, Vietnam), with approval No. 208/PCT-HĐĐĐ.

Funding/Support: This study did not receive any funding in any form.

Informed Consent: Written informed consent was obtained from parents or legal guardians before data collection.

References

1. Bryce J, Boschi-Pinto C, Shibuya K, Black RE; WHO Child Health Epidemiology Reference Group. WHO estimates of the causes of death in children. *Lancet*. 2005;**365**(9465):1147-52. [PubMed ID: 15794969]. https://doi.org/10.1016/S0140-6736(05)71877-8.
2. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;**372**(9):835-45. [PubMed ID: 25714161].

[PubMed Central ID: PMC4697461]. https://doi.org/10.1056/NEJMoa1405870.

3. Adegbola RA, Falade AG, Sam BE, Aidoo M, Baldeh I, Hazlett D, et al. The etiology of pneumonia in malnourished and well-nourished Gambian children. *Pediatr Infect Dis J*. 1994;**13**(11):975-82. [PubMed ID: 7845751]. https://doi.org/10.1097/00006454-199411000-00008.
4. World Health Organization. Guidelines for the Management of Common Childhood Illnesses. *Pocket Book of Hospital Care for Children*. 2nd ed. Geneva: World Health Organization; 2013.
5. Shann F. Etiology of severe pneumonia in children in developing countries. *Pediatr Infect Dis*. 1986;**5**(2):247-52. [PubMed ID: 3952013]. https://doi.org/10.1097/00006454-198603000-00017.
6. Collins S, Vickers A, Ladhani SN, Flynn S, Platt S, Ramsay ME, et al. Clinical and Molecular Epidemiology of Childhood Invasive Nontypeable Haemophilus influenzae Disease in England and Wales. *Pediatr Infect Dis J*. 2016;**35**(3):e76-84. [PubMed ID: 26569188]. https://doi.org/10.1097/INF.0000000000000996.
7. Falade AG, Mulholland EK, Adegbola RA, Greenwood BM. Bacterial isolates from blood and lung aspirate cultures in Gambian children with lobar pneumonia. *Ann Trop Paediatr*. 1997;**17**(4):315-9. [PubMed ID: 9578790]. https://doi.org/10.1080/02724936.1997.11747904.
8. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax*. 2011;**66 Suppl 2**:ii1-23. [PubMed ID: 21903691]. https://doi.org/10.1136/thoraxjnl-2011-200598.
9. Messinger AI, Kupfer O, Hurst A, Parker S. Management of Pediatric Community-acquired Bacterial Pneumonia. *Pediatr Rev*. 2017;**38**(9):394-409. [PubMed ID: 28864731]. https://doi.org/10.1542/pir.2016-0183.
10. Smith-Vaughan HC, Chang AB, Sarovich DS, Marsh RL, Grimwood K, Leach AJ, et al. Absence of an important vaccine and diagnostic target in carriage- and disease-related nontypeable Haemophilus influenzae. *Clin Vaccine Immunol*. 2014;**21**(2):250-2. [PubMed ID: 24285816]. [PubMed Central ID: PMC3910944]. https://doi.org/10.1128/CVI.00632-13.
11. Marshall AS, Barker CI, Pulickal AS, Kibwana E, Gautam SC, Clutterbuck EA, et al. The seroepidemiology of Haemophilus influenzae type b prior to introduction of an immunization programme in Kathmandu, Nepal. *PLoS One*. 2014;**9**(1). e85055. [PubMed ID: 24465475]. [PubMed Central ID: PMC3898912]. https://doi.org/10.1371/journal.pone.0085055.
12. Yoshida LM, Nguyen HA, Watanabe K, Le MN, Nguyen AT, Vu HT, et al. Incidence of radiologically-confirmed pneumonia and Haemophilus influenzae type b carriage before Haemophilus influenzae type b conjugate vaccine introduction in Central Vietnam. *J Pediatr*. 2013;**163**(1 Suppl):S38-43. [PubMed ID: 23773592]. https://doi.org/10.1016/j.jpeds.2013.03.029.
13. Benet T, Sanchez Picot V, Messaoudi M, Chou M, Eap T, Wang J, et al. Microorganisms Associated With Pneumonia in Children <5 Years of Age in Developing and Emerging Countries: The GABRIEL Pneumonia Multicenter, Prospective, Case-Control Study. *Clin Infect Dis*. 2017;**65**(4):604-12. [PubMed ID: 28605562]. [PubMed Central ID: PMC7108107]. https://doi.org/10.1093/cid/cix378.
14. Stralin K, Herrmann B, Abdeldaim G, Olcen P, Holmberg H, Molling P. Comparison of sputum and nasopharyngeal aspirate samples and of the PCR gene targets lytA and Spn9802 for quantitative PCR for rapid detection of pneumococcal pneumonia. *J Clin Microbiol*. 2014;**52**(1):83-9. [PubMed ID: 24153121]. [PubMed Central ID: PMC3911438]. https://doi.org/10.1128/JCM.01742-13.
15. Chee E, Huang K, Haggie S, Britton PN. Systematic review of clinical practice guidelines on the management of community acquired pneumonia in children. *Paediatr Respir Rev*. 2022;**42**:59-68. [PubMed ID: 35210170]. https://doi.org/10.1016/j.prrv.2022.01.006.
16. Rees CA, Kuppermann N, Florin TA. Community-Acquired Pneumonia in Children. *Pediatr Emerg Care*. 2023;**39**(12):968-76. [PubMed ID: 38019716]. https://doi.org/10.1097/PEC.0000000000003070.
17. Shann F, Gratten M, Germer S, Linnemann V, Hazlett D, Payne R. Aetiology of pneumonia in children in Goroka Hospital, Papua New Guinea. *Lancet*. 1984;**2**(8402):537-41. [PubMed ID: 6147602]. https://doi.org/10.1016/s0140-6736(84)90764-5.
18. Kalies H, Siedler A, Grondahl B, Grote V, Milde-Busch A, von Kries R. Invasive Haemophilus influenzae infections in Germany: impact of non-type b serotypes in the post-vaccine era. *BMC Infect Dis*. 2009;**9**:45. [PubMed ID: 19379490]. [PubMed Central ID: PMC2678273]. https://doi.org/10.1186/1471-2334-9-45.
19. Adams WG, Deaver KA, Cochi SL, Plikaytis BD, Zell ER, Broome CV, et al. Decline of childhood Haemophilus influenzae type b (Hib) disease in the Hib vaccine era. *JAMA*. 1993;**269**(2):221-6. [PubMed ID: 8417239].
20. Gkentzi D, Slack MP, Ladhani SN. The burden of nonencapsulated Haemophilus influenzae in children and potential for prevention. *Curr Opin Infect Dis*. 2012;**25**(3):266-72. [PubMed ID: 22561999]. https://doi.org/10.1097/QCO.0b013e3283531oa4.
21. World Health Organization. WHO position paper on Haemophilus influenzae type b conjugate vaccines. (Replaces WHO position paper on Hib vaccines previously published in the Weekly Epidemiological Record. *Wkly Epidemiol Rec*. 2006;**81**(47):445-52. [PubMed ID: 17124755].
22. Slack MPE. The evidence for non-typeable Haemophilus influenzae as a causative agent of childhood pneumonia. *Pneumonia (Nathan)*. 2017;**9**:9. [PubMed ID: 28702311]. [PubMed Central ID: PMC5483294]. https://doi.org/10.1186/s41479-017-0033-2.
23. Tran Quang K, Tran Do H, Pham Hung V, Nguyen Vu T, Tran Xuan B, Larsson M, et al. Study on the co-infection of children with severe community-acquired pneumonia. *Pediatr Int*. 2022;**64**(1). e14853. [PubMed ID: 34661955]. https://doi.org/10.1111/ped.14853.
24. Slack MPE. A review of the role of Haemophilus influenzae in community-acquired pneumonia. *Pneumonia (Nathan)*. 2015;**6**:26-43. [PubMed ID: 31641576]. [PubMed Central ID: PMC5922337]. https://doi.org/10.15172/pneu.2015.6/520.
25. Bamberger EE, Ben-Shimol S, Abu Raya B, Katz A, Givon-Lavi N, Dagan R, et al. Pediatric invasive Haemophilus influenzae infections in Israel in the era of Haemophilus influenzae type b vaccine: a nationwide prospective study. *Pediatr Infect Dis J*. 2014;**33**(5):477-81. [PubMed ID: 24445822]. https://doi.org/10.1097/INF.0000000000000193.
26. Rees CA, Basnet S, Gentile A, Gessner BD, Kartasasmita CB, Lucero M, et al. An analysis of clinical predictive values for radiographic pneumonia in children. *BMJ Glob Health*. 2020;**5**(8). [PubMed ID: 32792409]. [PubMed Central ID: PMC7430338]. https://doi.org/10.1136/bmjgh-2020-002708.
27. Nathan AM, Teh CSJ, Jabar KA, Teoh BT, Tangaperumal A, Westerhout C, et al. Bacterial pneumonia and its associated factors in children from a developing country: A prospective cohort study. *PLoS One*. 2020;**15**(2). e0228056. [PubMed ID: 32059033]. [PubMed Central ID: PMC7021284]. https://doi.org/10.1371/journal.pone.0228056.
28. Florin TA, Ambroggio L, Brokamp C, Zhang Y, Rattan M, Crotty E, et al. Biomarkers and Disease Severity in Children With Community-Acquired Pneumonia. *Pediatrics*. 2020;**145**(6). [PubMed ID: 32404432]. [PubMed Central ID: PMC7263054]. https://doi.org/10.1542/peds.2019-3728.