Italian Journal of Pediatrics

RESEARCH

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Co-infection in unvaccinated infants with acute pertussis in Western China (2018–2019): pathogen distribution and impact on disease severity

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Abstract

Background Co-infections in pertussis patients are common, but there has been limited research on the distribution of co-infecting pathogens and their impact on disease severity in infant patients remaining unvaccinated against pertussis. This study aims to investigate the pathogen distribution in unvaccinated infants with acute pertussis and explore how the number and type of co-infecting pathogens influence disease severity.

Method This cross-sectional study analyzed clinical data from 302 unvaccinated infants diagnosed with acute pertussis in western China. We compared clinical variables across different co-infection groups (bacteria, viruses, bacterial-viral combinations) and by the number of co-infecting pathogens (0, 1, ≥ 2).

Results Of the 302 patients, 121 (40.1%) were infected solely with *Bordetella pertussis*, while 181 (59.9%) had co-infections with other pathogens. The most common co-infections were bacterial (93 of 139 cases), particularly Gram-negative bacteria, followed by viral co-infections, mainly parainfluenza virus type-3 (PIV-3), in 71.3% of viral cases. The number of co-infecting pathogens was positively associated with longer hospital stays, more severe pneumonia, and higher incidence of respiratory failure ($P < 0.05$). Notably, bacterial co-infections were associated with more severe clinical outcomes than viral co-infections, with significant differences in hospitalization duration, as well as in peak white blood cell and lymphocyte counts ($P < 0.05$). No significant differences were observed in co-infection types or pathogen numbers across different age groups.

Conclusion Co-infections are prevalent among unvaccinated infants with acute pertussis in western China. Bacterial and viral pathogens are the most common co-infecting agents, and disease severity increases with the number of co-infecting pathogens. Bacterial co-infections may lead to more severe outcomes compared to viral co-infections, underscoring the need for targeted diagnostic and therapeutic strategies.

Keywords Co-infection, Unvaccinated, Infants, Pertussis, Severity

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Introduction

Pertussis (Whooping Cough), caused by *Bordetella pertussis*, is a respiratory infection and the fifth leading vaccine-preventable cause of infectious death in children worldwide [1]. Due to widespread vaccination, its incidence and mortality have significantly decreased. However, a subset of infants under one year of age remain unvaccinated against pertussis for various reasons, making them highly susceptible to *Bordetella pertussis* and other pathogens due to their immature immune systems.

In this vulnerable population, both bacterial [2] and respiratory viral [3] co-infections are frequently observed, often involving pathogens such as *respiratory syncytial virus* (*RSV*), *parainfluenza virus type 3* (*PIV-3*), and *adenovirus* [4, 5, 6, 7]. The prevalence and types of co-infections reported in previous studies vary substantially. For instance, Frassanito et al. [8] reported that 47% of pertussis patients under six months of age experienced mixed infections, predominantly with *rhinoviruses*. Likewise, Liu et al. [9] identified *Mycoplasma pneumoniae* as the most commonly detected co-infecting pathogen, with a positive detection rate of 45.6% among hospitalized children with respiratory infections.

Although many studies have analyzed the incidence and distribution of co-infections in pertussis, few have focused on unvaccinated infants and the impact of co-infections on disease severity. Since co-infections are believed to exacerbate the severity of pertussis [10–11], understanding their role is critical for refining diagnostic and therapeutic strategies. This study aims to investigate the distribution of co-infecting pathogens and evaluate the impact of co-infection on disease severity in unvaccinated infants with acute pertussis. By focusing on a high-risk subgroup of unvaccinated infants in western China, our research provides essential insights into the clinical burden of pertussis co-infections and may help inform hospital management strategies and targeted vaccination efforts.

Materials and methods

Patient selection

This retrospective cross-sectional study was conducted at the Children's Hospital of Chongqing Medical University. A total of 302 patients under one year of age, diagnosed with pertussis between April 1, 2018, and July 31, 2019, were enrolled. Pertussis diagnosis was established based on clinical signs and confirmed via PCR testing, with all patients also undergoing pertussis toxin immunoglobulin G (PT-IgG) testing. Anti-PT IgG levels were detected using commercially available ELISA kits (Zhengzhou Yite, China), following the manufacturer's instructions. The results were expressed in international units per mini-liter (IU/ml), and testing was conducted within three weeks of cough onset. Patients with severe cardiac or pulmonary diseases or other serious underlying conditions were excluded from the study. Clinical data for each patient, including gender, age of onset, length of hospital stay, peak heart rate (beats/min), peak respiratory rate (breaths/min), complications, C-reactive protein (CRP) levels, procalcitonin (PCT) levels, co-infection status, and results of peripheral blood cell analysis, were collected using the big data platform and electronic medical records from the hospital information system. The study received approval from the Ethics Committee of the Children's Hospital of Chongqing Medical University and adhered to the principles of the Helsinki Declaration. To protect patient privacy, data were collected by clinic ID numbers rather than patient names, and informed consent was waived.

Variables recorded and definitions

Pneumonia was diagnosed according to the radiologists' report based on pulmonary infiltrates or opacities in lung scan images. Severe pneumonia was defined as pneumonia with the co-occurrence of respiratory failure; Respiratory failure was defined by the presence of clinical signs of hypoxia and an increased breathing rate (≥ 60 breaths per minute for infants under one year). Pulmonary hypertension was indicated by an echocardiogram showing increased pulmonary artery pressure. Pulmonary consolidation was defined based on imaging evidence of consolidative changes. Cardiovascular failure was diagnosed based on an increased heart rate (≥ 160 beats per minute for infants under one year) and echocardiogram findings suggesting impaired cardiac function. Bacterial co-infection was defined as a positive sputum culture identifying relevant bacteria, while viral co-infection was defined by a positive respiratory pathogen antigen test. Elevated CRP was defined as levels exceeding 8 mg/L, and elevated PCT was defined as levels exceeding 0.5 ng/mL.

Statistical analysis

Statistical analyses were performed using SPSS software version 25. Descriptive statistics for non-normally distributed data are presented as median values with interquartile ranges (IQR). Comparisons between two groups were performed using the Mann-Whitney U test, while comparisons across multiple groups were conducted using the Kruskal-Wallis rank test. Categorical data are expressed as percentages (%), and differences between groups were assessed using the chi-square test. A P-value of less than 0.05 was considered statistically significant.

Results

General and clinical characteristics of patients

The demographic characteristics of the 302 participants are shown in Table 1, with 130 (43.05%) being females

Table 1 Clinical data of the 302 patients

Clinical characteristics	Total (*N* = 302)
Age of onset (day), median (IQR)	78 (22, 353)
Gender (female, n, %)	130 (43.05%)
Hospital length of stay, median (IQR)	7 (1, 32)
Pertussis Toxin IgG antibodies, IU/ml, median (IQR)	2.73 (0.00, 219.76)
WBC count, highest cells×10^3/μL, median (IQR)	15.41 (4.44, 93.52)
Lymphocyte count, highest cells×10^3/μL, median (IQR)	10.92 (2.22, 43.95)
Raised C-reactive protein (n, %)	16 (5.30%)
Raised Procalcitonin (n, %) > 0.5 ng/ml	10 (3.31%)
Highest respiratory rate (breaths/min)	42 (21, 70)
Highest heart rate (beats/min)	130 (105, 198)
Pneumonia (n, %)	233 (77.15%)
Severe Pneumonia (n, %)	29 (9.60%)
Respiratory failure (n, %)	27 (8.94%)

Table 2 Comparison of single infections with different numbers of co-infections

	Single pertussis infection	One co-infection	Two and more co-infection	*P* value
	121 (40.07%)	134 (44.37%)	47 (15.56%)	
Age of onset (day), median (IQR)	81 (13, 293)	74 (14, 353)	78 (22, 340)	0.805
Hospital length of stay, median (IQR)	7 (1, 24)	7.5 (1, 31)	10 (3, 32)	0.001
Gender (female, n, %)	52 (42.98%)	55 (41.04%)	23 (48.94%)	0.643
Pertussis Toxin IgG antibodies, IU/ml, median (IQR)	0.98 (0.00, 170.64)	3.83 (0.00, 219.76)	2.93 (0.00, 167.43)	0.894
WBC count, highest cells×10^3/μL, median (IQR)	16.75 (6.16, 59.5)	14.12 (4.44, 93.52)	16.68 (7.39, 50.51)	0.699
Lymphocyte count, highest cells×10^3/μL, median (IQR)	12.48 (2.64, 42.25)	10.03 (3.15, 43.95)	12.4 (2.22, 37.8)	0.172
Raised C-reactive protein (n, %)	1 (0.83%)	13 (9.70%)	2 (4.26%)	/
Raised Procalcitonin (n, %), >0.5 ng/ml	1 (0.83%)	6 (4.48%)	3 (6.38%)	/
Highest respiratory rate (breaths/min)	42 (21, 68)	41 (30, 70)	42 (31, 68)	0.117
Highest heart rate (beats/min)	131 (105, 198)	130 (112, 168)	130 (118, 163)	0.570
Pneumonia (n, %)	91 (75.21%)	101 (75.37%)	41 (87.23%)	0.201
Severe Pneumonia (n, %)	5 (4.13%)	17 (12.69%)	7 (14.89%)	0.028
Respiratory failure (n, %)	5 (4.13%)	15 (11.19%)	7 (14.89%)	0.042

and 172 (56.95%) being males. The median age of onset was 78 days (IQR: 22–353 days). The median level of PT-IgG antibody was 2.73 IU/ml (0.00–219.76 IU/ml). The median peripheral blood white blood cell (WBC) count was 15.42×10^3/μL ($4.44–93.52 \times 10^3$/μL), and the median lymphocyte count was 10.92×10^3/μL ($2.22–43.95 \times 10^3$/μL). Acute-phase proteins, such as CRP and PCT, were elevated in only a small proportion of patients, with CRP elevated in 5.30% and PCT in 3.31%. The highest respiratory rate (breaths/min) and highest heart rate (beats/min) were 42 (21–70) and 130 (105–198), respectively. Pneumonia was the most common complication, occurring in 77.15% of patients, while severe pneumonia and respiratory failure occurred in 9.60% and 8.94% of patients.

Clinical and laboratory profile comparison in single versus co-infected patients

Table 2 presents the clinical and laboratory findings for patients with single *Bordetella pertussis* infection and those with co-infections involving different numbers of pathogens. Among the 302 patients, 121 (40.07%) were infected solely with *Bordetella pertussis*, 134 (44.37%) had one additional co-infecting pathogen, and 47 (15.56%) had two or more co-infecting pathogens, underscoring the high prevalence of co-infections among unvaccinated infants with acute pertussis. No significant differences were observed in gender, age of onset, antibody levels, peripheral blood WBC count, lymphocyte count, peak respiratory rate, peak heart rate, or pneumonia incidence among the three groups. However, hospitalization duration significantly increased with the number of co-infecting pathogens (median (IQR): 7 days (1–24), 7.5 (1–31), and 10 (3–32), respectively; $P = 0.001$); similarly, the incidence rates of severe pneumonia (4.13%, 12.69%, and 14.89%, respectively; $P = 0.028$) and respiratory failure (4.13%, 11.19%, and 14.89%, respectively; $P = 0.042$) also increased significantly with the number of co-infecting pathogens, which suggesting that co-infection, particularly with an increased number of pathogens, was associated with prolonged hospital stays and a higher frequency of severe respiratory complications in unvaccinated infants with acute pertussis.

Clinical and laboratory profile comparison in patients Co-infected with Bacteria and viruses

Table 3 shows the clinical and laboratory characteristics of patients with bacterial, viral, and bacterial-viral co-infections. Among the 174 patients with co-infections, bacterial co-infections were the most prevalent, accounting for 55.17% of cases ($n = 96$), followed by viral co-infections at 24.14% and combined bacterial-viral co-infections at 20.69%. There were no significant differences among the three groups in terms of gender, age of

Table 3 Comparison of viral and/or bacterial infections

	Bacteria co-infection	Virus co-infection	Bacteria-Virus co-infection	*P* value
	96 (55.17%)	42 (24.14%)	36 (20.69%)	
Age of onset (day), median (IQR)	72 (17, 340)	71.5 (14, 322)	80 (29, 214)	0.754
Hospital length of stay, median (IQR)	8 (1, 32) [a]	7 (4, 19) [b]	10 (3, 32)	0.115
Gender (female, n, %)	44 (45.8%)	12 (28.6%)	18 (50.00%)	0.100
Pertussis Toxin IgG antibodies, IU/ml, median (IQR)	2.66 (0.00, 219.76)	10.11 (0.00, 214.95)	2.57 (0.00, 167.43)	0.610
WBC count, highest cells×10^3/μL, median (IQR)	15.41 (5.5, 93.52) [c]	12.67 (4.44, 34.63)	16.03 (7.39, 50.51)	0.059
Lymphocyte count, highest cells×10^3 /μL, median (IQR)	10.77 (3.92, 43.95) [d]	8.49 (3.15, 24.66)	12.39 (2.22, 12.39)	0.096
Raised C-reactive protein (n, %)	13 (13.5%)	0 (0.00%)	1 (2.8%)	/
Raised Procalcitonin (n, %), >0.5 ng/ml	7 (7.29%)	0 (0.00%)	2 (5.56%)	/
Highest respiratory rate (breaths/min)	40 (30, 70)	42 (32, 60)	43.5 (31, 68)	0.102
Highest heart rate (beats/min)	130 (112, 168)	132 (115, 159)	130 (118, 163)	0.617
Pneumonia (n, %)	74 (77.1%)	34 (81.0%)	34 (86.1%)	0.505
Severe Pneumonia (n, %)	14 (14.6%)	5 (11.9%)	5 (13.9%)	0.915
Respiratory failure (n, %)	12 (12.5%)	5 (11.9%)	5 (13.9%)	0.964

Table Note: "a" indicates the duration of hospitalization between bacterial and viral infections ($P=0.018$), "b" indicates the duration of hospitalization between viral and viral-bacterial co-infections ($P=0.036$); "c" indicates the highest peripheral white blood cell count between bacterial and viral infections ($P=0.027$); "d" indicates the highest peripheral lymphocyte count between bacterial and viral infections ($P=0.011$)

onset, antibody levels, peak respiratory rate, peak heart rate, pneumonia incidence, severe pneumonia, or respiratory failure. However, hospitalization duration differed significantly between patients with bacterial and viral co-infections (median (IQR): 8 days (1–32) versus 7 (4–19), $P=0.018$) and between those with viral and bacterial-viral co-infections (7 (4–19) versus 10 (3–32), $P=0.036$), though no significant difference was observed between bacterial and bacterial-viral co-infections. The peak WBC and lymphocyte counts in peripheral blood decreased gradually from bacterial-viral to bacterial to viral co-infections, with significant higher counts in bacterial co-infections than in viral co-infections for both WBC (15.41×10^3/μL (5.5–93.52) versus 12.67×10^3/μL (4.44–34.63), $P=0.027$) and lymphocyte counts (10.77×10^3/μL (3.92–43.95) versus 8.49×10^3/μL (3.15–24.66), $P=0.011$).

Table 4 Comparison of bacterial and/or viral co-infections across different age

Pathogen	0–3	3–6	6–12	*P* value
	N=110	*N*=52	*N*=12	
Bacteria co-infection	62 (56.4%)	25 (48.1%)	9 (75.0%)	0.220
Virus co-infection	26 (23.6%)	14 (26.9%)	2 (16.7%)	0.740
Bacteria-Virus co-infection	22 (20.0%)	13 (25.0%)	1 (8.3%)	0.420

Table 5 Comparison of single-infections and co-infections across different ages

Co-infection	0–3	3–6	6–12	*P* value
	N=185	*N*=90	*N*=27	
Single pertussis infection	73 (39.5%)	34 (37.8%)	14 (51.9%)	0.409
One co-infection	84 (45.4%)	39 (43.3%)	11 (40.7%)	0.877
Two and more co-infection	28 (15.1%)	17 (18.9%)	2 (7.4%)	0.341

Comparison of Co-Infection patterns across different age groups

Table 4 presents the co-infection status with different type of pathogens across the three age groups (0–3 months, 3–6 months, and 6–12 months). There were no significant differences in the incidence of bacterial, viral, or bacterial-viral co-infections among the age groups. However, bacterial infections were the most common co-infecting pathogens in all age groups, with the highest prevalence observed in the 6–12 month age group.

The co-infection status with different numbers of pathogens across the age groups is shown in Table 5. There were no significant differences in the incidence of single *Bordetella pertussis* infection, one co-infecting pathogen, or two or more co-infecting pathogens among the three age groups. Co-infection with one additional pathogen was most common in infants aged 0–6 months, while single *Bordetella pertussis* infection was most frequent in those aged 6–12 months.

Distribution of detected pathogens

Among the 302 patients, 181 were found to have pathogens other than *Bordetella pertussis* (Fig. 1). Of these, 139 patients had bacterial infections, with Gram-negative bacteria being predominant (93 cases) compared to Gram-positive bacteria (46 cases). There were 80 viral infections involving four main types of viruses: 57 cases of *PIV-3*, 14 cases of *RSV*, 7 cases of *adenovirus*, and 2 cases of *influenza A*. Additionally, less common

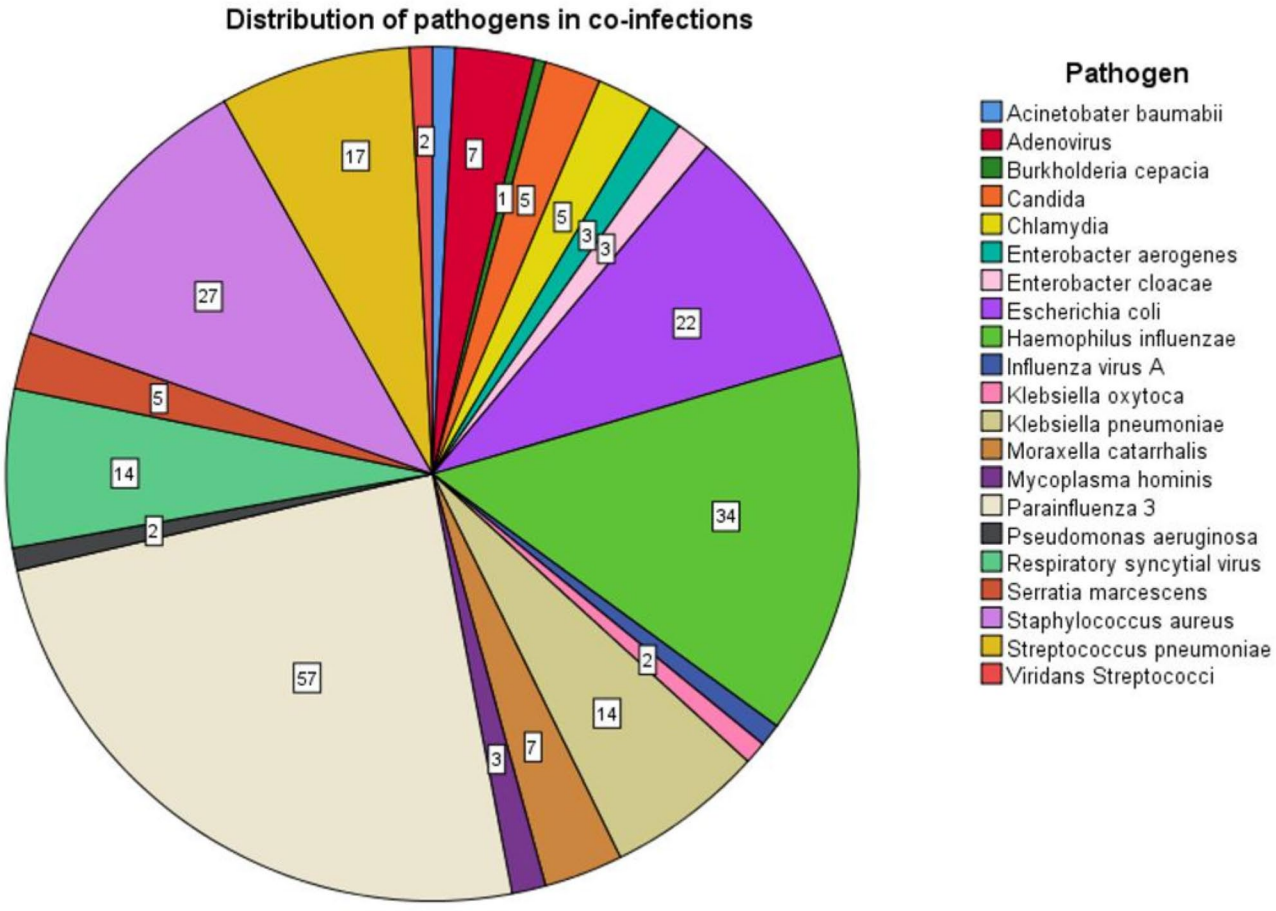

Fig. 1 Distribution of pathogens in co-infections

pathogens detected included *Candida* (5 cases), *Mycoplasma* (3 cases), and *Chlamydia* (5 cases).

Discussion

Pertussis, caused by *Bordetella pertussis*, remains a significant respiratory infectious disease, especially among vulnerable populations like infants. In this study, we found that co-infections were highly prevalent among unvaccinated infants with acute pertussis in western China, with 59.9% of cases having at least one co-infecting pathogen. Bacterial co-infections were most common, especially involving Gram-negative bacteria, while viral co-infections, particularly PIV-3, were also frequent. Furthermore, we observed that an increasing number of co-infecting pathogens was associated with more severe clinical outcomes, such as longer hospital stays and more frequent respiratory failure, with bacterial co-infections associated with more severe outcomes compared to viral infections.

As a vaccine-preventable disease, widespread pertussis vaccination has significantly reduced both the incidence and mortality of pertussis worldwide. However, significant gaps in vaccination coverage persist, particularly in resource-limited regions, leaving a considerable number of people unvaccinated. According to the World Health Organization, globally in 2023, approximately 14.5 million children had not received any pertussis vaccination, and the coverage of a third dose of the diphtheria, pertussis, and tetanus (DPT) vaccine stalled at 84% [12]. This suggests that a significant number of children are still not immunologically protected. Despite DPT vaccination coverage exceeding 95% in China [13], regions like western China continue to face persistent challenges due to limited healthcare access and vaccine hesitancy. Our findings from 302 unvaccinated infants with pertussis infection underline the critical vulnerability of this group, highlighting the urgent need for targeted interventions in under-vaccinated populations. These efforts are particularly important in areas with limited access to healthcare and vaccination services, where co-infections are likely to exacerbate the disease burden.

Co-infections are frequently observed in patients with pertussis, particularly during the acute phase. Although it remains unclear whether co-infections are associated with specific pathogenic mechanisms [7, 14], current research suggests that PT plays a significant role in

co-infections. Studies have found that PT has immunosuppressive effects on both innate and adaptive immunity to *B. pertussis* infection [15, 16, 17]. It is speculated that the continuous action of PT on the immune system in patients with *B. pertussis* inhibits the body's immune function, making viral infections more likely [18–19]. Conversely, respiratory viruses, including influenza viruses, may facilitate bacterial co-infections by promoting the activation of type I interferons and the release of pro-inflammatory cytokines [20–21]. Additionally, the overlap in seasonal prevalence of pertussis with some viruses may also contribute to the occurrence of co-infections.

As noted in the literature, co-infections are independently associated with worse disease outcomes, including prolonged hospitalizations and more severe symptoms compared to single infections [3, 10, 22]. In our study, the number of co-infecting pathogens was positively correlated with longer hospital stays and increased incidence rates of severe complications, such as severe pneumonia and respiratory failure ($P = 0.028$ and 0.042, respectively), reinforcing the notion that co-infections may exacerbate the severity of pertussis. Our findings align with those of prior studies, which have shown that pertussis, when complicated by co-infections, often leads to more severe clinical manifestations and prolonged recovery times.

Pertussis in infants and young children is frequently characterized by a significant rise in circulating WBC [23–24]. In our study, the peak WBC and lymphocyte counts in the peripheral blood were lowest in the viral infection group, followed by the bacterial infection group, and highest in the bacterial combined with viral infection group. While these differences did not reach statistical significance ($P = 0.059$ and 0.096, respectively), they suggest that co-infections may influence immune responses in ways that are not fully captured by WBC and lymphocyte counts alone. In addition, the levels of WBC and lymphocytes appeared to be primarily reflective of *B. pertussis* infection, with minimal impact from co-infections. Therefore, these markers may not be reliable as indicators for distinguishing mixed infections in clinical practice.

The distribution of co-infecting pathogens in our study aligns with findings from others. Most domestic and international studies have found RSV, PIV-3, and adenovirus to be common pathogens in co-infections [4, 5, 6, 7]. There are also research reports that 47% of pertussis patients under six months of age have mixed infections, primarily rhinoviruses [8]. Liu and colleagues reported that the positive detection rate of *Mycoplasma pneumoniae* reached 45.6% in hospitalized children with respiratory infections, making it the most common pathogen in mixed infections [9]. In our study, 181 patients were found to have additional pathogens, including 139 bacterial infections, with 93 cases involving Gram-negative bacteria and 46 involving Gram-positive bacteria, indicating a predominance of Gram-negative infections. Besides, 80 patients had viral infections, involving four main types of viruses: 57 cases of PIV-3, 14 cases of RSV, 7 cases of adenovirus; and 2 cases of influenza A virus. The distribution of pathogens was mainly bacterial infections, followed by mixed viral infections, with PIV-3 being the most common among mixed viruses, followed by RSV, adenovirus, and influenza A. This is consistent with Skoff's [2] finding that mixed bacterial infections are the most common. Patients with mixed viral infections are also numerous and should not be ignored in clinical practice, since co-infections with respiratory viruses are frequent in infants [3].

The frequent occurrence of co-infections underscores the complexity of managing pertussis in infants and calls for comprehensive diagnostic approaches. A high-resolution pathogen profiling, such as the one conducted in our study, can serve as a valuable tool for the development of region-specific rapid diagnostic panels, prioritizing pathogens with the highest prevalence (e.g., Gram-negative bacteria and PIV-3). The accurate identification of co-infections in this study relied on multiplex PCR and sequencing, which are essential to distinguish pathogens with overlapping clinical symptoms (e.g., *B. pertussis* vs. *Mycoplasma pneumoniae*). While these methods require centralized laboratory infrastructure, they provide critical epidemiological data on regional pathogen prevalence, informing the development of more cost-effective, simplified rapid tests targeting high-priority pathogens. To bridge the gap between research and clinical practice in low-resource settings, we propose a tiered diagnostic strategy: initial screening with low-cost lateral flow assays, followed by confirmatory testing in regional hubs using the protocols described here.

Despite pertussis being a bacterial infection that causes necrotizing bronchitis (an aggressive infectious disease), we found that *B. pertussis* does not induce the production of PCT, a biomarker often associated with bacterial infections. This may be because *B. pertussis* does not affect the specific tissues responsible for PCT production [25]. Therefore, we found that the rate of significant PCT elevation was low in both single and co-infection groups, even among patients with bacterial co-infections. This contrasts with other studies that suggest PCT is an independent risk factor for mixed bacterial infections in children with pertussis, where the risk of mixed bacterial infections increases with elevated levels of PCT [26].

In conclusion, our study highlights the high prevalence of co-infections among unvaccinated infants with acute pertussis in western China, emphasizing the influence of co-infecting pathogens in exacerbating disease severity. Bacterial co-infections, particularly those involving

Gram-negative bacteria, were most common, while viral infections, especially PIV-3, were also frequently observed. The presence of multiple pathogens was associated with worse clinical outcomes, including longer hospital stays and increased incidence of severe pneumonia and respiratory failure. These findings underscore the urgent need for targeted vaccination and diagnostic interventions, particularly in resource-limited regions, where co-infections are likely to amplify the disease burden. The development of cost-effective diagnostic panels for the most common pathogens, as well as training programs to recognize severe co-infection signs (e.g., prolonged hospitalization) may improve early detection and health management, ultimately reducing morbidity and mortality in vulnerable populations.

Acknowledgements
We are thankful to all the participants who took part and contributed to this study.

Author contributions
C Gan: Conceptualization, Data curation, Statistical analysis, Writing–original draft; YY Wu: Conceptualization, Supervision, Writing–review & editing. All authors contributed meaningfully to this manuscript and approved the final version.

Funding
This study was supported by the Natural Science Foundation of China (No. 82401838) and by the Natural Science Foundation of Chongqing, China (CSTB2023NSCQ-BHX0042).

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors report no conflicts of interest in this work. All authors have read and approved the manuscript.

Received: 15 January 2025 / Accepted: 23 March 2025
Published online: 09 April 2025

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