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Evolution of acute infection with atypical bacteria in a prospective cohort of children with community-acquired pneumonia receiving amoxicillin

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Background: Atypical bacteria are treatable causative agents of community-acquired pneumonia (CAP). However, there is no conclusive evidence that a child with CAP should receive empirical treatment against such agents.

Objectives: We assessed the possibility of association between clinical failure and acute infection by these bacteria among children with CAP treated with amoxicillin.

Patients and methods: Patients aged 2–59 months with non-severe CAP received amoxicillin during prospective follow-up. Acute and convalescent blood samples were collected. Probable acute infection by *Mycoplasma pneumoniae* (specific IgM antibodies), by *Chlamydia pneumoniae* or *Chlamydia trachomatis* (specific IgM antibodies and/or IgG/IgA titre change) was investigated. Outcomes were assessed during follow-up at 2, 5 and 14–28 days. Treatment failure included development of danger signs, persistent fever, tachypnoea or death. ClinicalTrials.gov: NCT01200706.

Results: Of 787 children, 86 (10.9%; 95% CI = 8.9%–13.3%) had acute *M. pneumoniae* infection. *C. pneumoniae* acute infection was found in 79 of 733 (10.8%; 95% CI = 8.7%–13.2%) and *C. trachomatis* was found in 3 of 28 (10.7%; 95% CI = 2.8%–26.5%) <6 months old. Among patients with or without treatment failure at 2 days, acute *M. pneumoniae* infection (11.7% versus 10.7%; $P = 0.7$), acute *C. pneumoniae* infection (8.5% versus 11.3%; $P = 0.3$) and acute *C. trachomatis* infection (16.7% versus 9.1%; $P = 0.5$) were found. No significant differences were found with regard to treatment failure at the 5 day evaluation. Overall, amoxicillin was substituted in 3.5% versus 2.7% among patients with or without acute infection by one of these bacteria ($P = 0.6$).

Conclusions: The overall substitution rate of amoxicillin was very low. It is not necessary to give an empirical non-β-lactam antibiotic as a first-line option to treat every child between 2 and 59 months old with non-severe CAP.

Introduction

Community-acquired pneumonia (CAP) remains one of the leading causes of childhood morbidity, both in developed and developing countries.[1,2] It also continues to be the most frequent cause of death in children <5 years of age worldwide.[3] It has been increasingly recognized that the aetiology of CAP comprises diverse infectious agents, such as typical bacteria (particularly *Streptococcus pneumoniae* and *Haemophilus influenzae*), atypical bacteria (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Chlamydia trachomatis*) and viruses.[4] As death due to CAP has been classically attributed to infection by *S. pneumoniae*,[5] international guidelines consensually recommend the use of β-lactam antibiotics to treat these patients as *S. pneumoniae* is the main target.[6] However, atypical bacteria are also treatable causes of CAP by using non-β-lactam antibiotics.[7] Conversely, there is no conclusive evidence that a child with CAP should receive first-choice treatment with an empirical non-β-lactam antibiotic.[8]

We assessed the possibility of association between clinical treatment failure and acute infection by atypical bacteria, in children with non-severe CAP treated with a β-lactam antibiotic (amoxicillin).

Patients and methods

Ethics

Before recruitment, written informed consent was obtained from the parents or legal guardians when those caregivers agreed to stay in the observation ward of the hospital with the child for the purpose of this study. This study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. It was approved by the Ethics Committee of the Federal University of Bahia (approval reference number 24/2006).

Study design and patient selection

From November 2006 to April 2011, patients aged between 2 and 59 months with non-severe CAP were prospectively followed-up in a randomized, triple-blinded clinical trial (ClinicalTrials.gov: NCT01200706) conducted at the Emergency Department of the Federal University Bahia Hospital, in Salvador, Northeast Brazil. Non-severe CAP was defined as the report of respiratory complaints, plus detection of lower respiratory findings, plus radiographic detection of pulmonary infiltrate/consolidation and the absence of chest indrawing or any danger sign (listed in the exclusion criteria below). All patients received amoxicillin (50 mg/kg/day): half received amoxicillin thrice daily and half received amoxicillin twice daily. In the region where this study was conducted, there was no penicillin resistance.[9] The pharmacy unit of the hospital was informed about the recruitment and independent pharmacists dispensed two bottles named Amoxicillin 1 and Amoxicillin 2: one bottle contained amoxicillin and the other contained placebo, according to the randomization sequence. The primary results of this trial have already been published.[10] Potentially eligible cases were identified by trained paediatricians based on the report of respiratory complaints and detection of lower respiratory findings, plus detection of pulmonary infiltrate/consolidation on chest radiograph (CXR) (frontal and lateral views) taken on admission and read by the paediatrician on duty. Exclusion criteria included the presence of lower-chest indrawing, danger signs (inability to drink, convulsions, somnolence, central cyanosis, grunting in a calm child), chronic debilitating diseases (anatomic abnormalities of the respiratory tract, cancer, chronic pulmonary illness besides asthma, immunological defects, progressing neurological disorders, psychomotor retardation, heart disease with clinical repercussion, haemoglobinopathy, liver or kidney disease), severe malnutrition, other concurrent infection, HIV-infected mother, hospitalization during the previous 7 days, amoxicillin or similar antibiotic use during the last 48 h, amoxicillin allergy, or history of aspiration. Eligible cases were recruited by one trained medical student, under the supervision of a senior paediatrician, who is a member of this research team and stayed on duty in the same Emergency Department to apply the eligibility criteria, present the informed consent and finally recruit the cases.

Procedures

Upon enrolment, a thorough examination was performed and data on demographics, clinical history and physical examination were registered in a predefined form. Amoxicillin (Prati-Donaduzzi) 250 mg/5 mL was bought by the hospital and the manufacturer was not aware or involved in this study.

Participants were followed-up twice a day by trained medical students, who also assisted drug administration, always under the supervision of a senior paediatrician from the research team. Reports of daily complaints and findings were recorded using a standardized form. Each child was discharged from hospital when there was no more fever and respiratory discomfort, supplied with sufficient Amoxicillin 1 and Amoxicillin 2 to complete 10 days of treatment, as according to national Brazilian guidelines.[11] The caregiver received the telephone number of the senior paediatrician and was advised to call if the patient presented any complaint. On the fifth day of treatment, the senior paediatrician called the caregiver to enquire about symptoms and interventions. A final follow-up examination was performed by the senior paediatrician 14 days after enrolment in the outpatient setting of the same hospital, when the second CXR (frontal and lateral views) was taken. If the child did not return on the initially scheduled day, the senior paediatrician called the family to re-schedule to prevent the child from being lost at follow-up. The CXR was sent to two independent paediatric radiologists who were blinded to clinical information. Radiographic findings were registered in accordance with standardized interpretation.[12] Radiologically diagnosed pneumonia was identified if there was agreement on the presence of pulmonary infiltrate/consolidation from two independent assessments. All data were registered on predefined forms. Altogether, two senior paediatricians and 27 medical students took part in this study. No change to the original protocol occurred after the trial commenced.

Blood samples were collected upon admission and at the 14 day follow-up visit when the respective serum samples were stored at −20°C. Probable acute infection by *M. pneumoniae* was investigated by searching for specific IgM antibodies using a commercial ELISA kit (Platelia; Bio-Rad, Marnes La Coquette, France) in the convalescent serum samples. The acute serum sample was used only if the convalescent serum sample had not been collected. These tests were performed at the Centro de Pesquisa Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Brazil. A probable acute infection by *C. pneumoniae* was investigated by searching for specific IgM, IgG and IgA antibodies using a commercial ELISA kit (Ani Labsystems Ltd, Vantaa, Finland) and was defined as the presence of IgM and/or ≥1.3/1.5-fold increase in IgG/IgA EIU value (according to the manufacturer's instructions). *C. trachomatis* IgG, IgM and IgA antibodies were studied by an in-house micro-immunofluorescence test.[13] A specific IgM response or ≥4-fold increase in IgG/IgA titre was indicative of probable acute *C. trachomatis* infection. These tests were performed at the Department of Virology, University of Helsinki, Finland. *C. trachomatis* infection was only searched for amongst children <6 months old. All laboratory tests were performed after the clinical trial had finished and laboratory personnel were blinded to any clinical data.

Definitions

Outcomes were defined *a priori*: treatment failure up to 2 days of treatment included death, development of danger signs, persistence of fever or tachypnoea; cumulative treatment failure up to 5 days after enrolment also included persistence of cough and recurrence of fever. Fever was defined as axillary temperature >37.5°C,[14] and tachypnoea as respiratory rate ≥50 breaths/min in children aged 2–11 months or respiratory rate ≥40 breaths/min in children from 12 months of age upwards.[15] The upper record in each day was considered in the analysis. Nutritional evaluation was performed by using the software 'Anthro' (WHO); malnutrition and severe malnutrition were defined as the Z-score for weight-for-age under −2.00 and under −3.00, respectively.[16]

Data entry and statistical analysis

Data were entered in the software EPI-INFO version 6.04 and analysed in SPSS (version 9.0). Excluded from the analysis were: participants excluded after randomization because they were found not to meet eligibility criteria (protocol violators); participants who abandoned or were withdrawn by legal guardians from the trial; or participants who developed serious adverse reactions that caused amoxicillin substitution. Continuous variables with a parametric distribution are presented as mean ± SD; those with a non-parametric distribution are presented as median (IQR). We calculated the frequency of (along with the respective 95% CI): acute infection by each studied bacterium, by at least one of the three studied bacteria, of treatment failure at 2 and 5 days of follow-up and of antibiotic substitution. Then, we compared the frequency of acute infection among patients with or without treatment failure and the frequency of antibiotic substitution among cases with or without acute infection by using Pearson χ^2 or Fisher Exact test, as appropriate. All tests were two-tailed and statistical

Table 1. Baseline characteristics of 787 children with non-severe CAP

Characteristics	Percentage	Median (IQR) length (days)
Demographics		
age <6 months	3.6	
age <1 year	20.2	
male	52.0	
History		
cough	97.5	5 (3–8)
fever	92.2	4 (2–5)
difficulty breathing	62.3	3 (2–5)
vomiting	45.2	2 (1–3)
wheezing	31.5	3 (2–5)
Physical examination		
rhonchi	64.9	
crackles	44.5	
tachypnoea	44.3	
fever	33.3	
wheezing	29.5	
reduced pulmonary expansion	8.5	
chest retraction	3.8	
non-severe malnutrition	3.3	

significance was considered at the 5% level. Sample size was estimated considering a smaller frequency of amoxicillin failure in cases without atypical bacterial infection of 10% and an expected difference of failure between cases with or without atypical bacterial infection of 5%. Thus, the sample size was estimated as 685 cases, considering a significance level of 0.05 (two-tailed) (95% CI) and power of 80%. Patients without investigation of infection by a specific atypical bacterium due to insufficient serum were excluded from the analysis only with regard to infection by this particular bacterium. Patients lost during the follow-up period were excluded from the analysis at the moment when they were lost. Herein, results from a *post-hoc* analysis are shown.

Results

A total of 820 patients were enrolled, of which 16 (2.0%) did not receive the intervention because they were mistakenly enrolled or the family withdrew the child immediately after enrolment ($n = 8$ each), 10 (1.2%) did not have blood samples collected, 4 (0.5%) were withdrawn and 3 (0.4%) developed serious adverse reaction (2 severe urticaria and 1 excessive vomiting) during the first 2 days of treatment. Therefore, this study group comprises 787 cases. The median (IQR) age was 25 (14–40) months and the median (IQR) disease duration prior to recruitment was 5 (4–8) days. The baseline characteristics of the study group are shown in Table 1.

Acute *M. pneumoniae* infection was diagnosed in 86 (10.9%; 95% CI = 8.9%–13.3%) of 787 cases. Acute *C. pneumoniae* infection was found in 79 (10.8%; 95% CI = 8.7%–13.2%) of 733 investigated patients. Acute *C. trachomatis* infection was found in 3 (10.7%; 95% CI = 2.8%–26.5%) of 28 cases <6 months old. Overall, 147 (20.1%; 95% CI = 17.3%–23.1%) of 731 cases investigated for these three bacteria had acute infection by at least one bacterium (18 patients had concomitantly positive tests for acute *M. pneumoniae* and acute *C. pneumoniae* infection). Of 787 patients included in the study group, 48 (6.1%) did not have blood samples collected on the 14 day follow-up visit. None died, none was admitted to an ICU and none had sepsis diagnosed. Failure at 2 days of treatment was registered in 162 (20.6%; 95% CI = 17.9%–23.5%) cases. The most common cause for treatment failure was persistence of tachypnoea. At the 5 day evaluation, an additional 23 (2.9%) patients were lost to follow-up resulting in the cumulative failure rate of (169 of 764) 22.1% (95% CI = 19.3%–25.2%). Table 2 shows the comparison of the frequency of acute infection by each bacterium or at least one of the studied bacteria between patients with or without treatment failure at 2 and 5 days of treatment.

On the 14 day follow-up evaluation, an additional 20 (2.6%) patients were lost to follow-up and 5 (0.7%) presented severe adverse reaction (four diarrhoea and one urticaria) that led to amoxicillin discontinuation. The mean interval between enrolment and this follow-up visit was 20±7 days [median (IQR) = 19 (16–22) days]. Of 739 evaluated patients, a CXR was not performed in 7 (0.9%); reading was discordant in 24 (3.2%) and concordant in 708 (95.8%); additionally, 9 (1.2%) CXR were concordantly evaluated as unreadable. The total frequency of CXR diagnoses at the follow-up visit was: normal CXR ($n = 621$; 88.8%), pneumonia ($n = 50$; 7.2%) and other radiological diagnoses ($n = 28$; 4.0%). There was no association between radiologically diagnosed pneumonia and acute infection by *M. pneumoniae* or *C. pneumoniae* (Table 3). None of the cases with an acute *C. trachomatis* infection had concordant radiologically diagnosed pneumonia.

Overall, 3.4% (25 of 739; 95% CI = 2.2%–4.9%) patients had amoxicillin discontinued due to treatment failure. These cases along with the respective reason for substitution and the subsequent antibiotics used are listed in Table S1 (available as Supplementary data at *JAC* Online). Indeed, one patient was receiving masked bottles of amoxicillin administered thrice daily and placebo administered twice daily when the intervention was discontinued and unmasked amoxicillin 250 mg/5 mL was given as 50 mg/kg/day divided into three daily doses; another patient had cystic fibrosis diagnosed during continuous outpatient follow-up because of persistence of tachypnoea, irrespective of antibiotic change. None of the cases with acute *C. trachomatis* infection had amoxicillin discontinued. Among those who did not interrupt the intervention, the mean length of intervention use was 10±1 days. Table 4 depicts the comparison of the frequency of amoxicillin substitution in patients with or without acute *M. pneumoniae* infection, or acute *C. pneumoniae* infection, or both.

There were two arms in the clinical trial: the frequencies of acute *M. pneumoniae*, *C. pneumoniae*, *C. trachomatis* or at least one of these three bacterial infections in each of the arms were, respectively, 10.2% versus 11.7% ($P = 0.5$), 12.7% versus 8.8% ($P = 0.09$), 14.3% versus 7.1% ($P = 1$) and 21.2% versus 19.0% ($P = 0.5$). The results of this clinical trial showed that oral amoxicillin (50 mg/kg/day) twice daily is as efficacious as thrice daily.[9]

Discussion

We did a prospective study enrolling a large sample of children diagnosed with CAP by paediatricians, by using standardized criteria. These patients were given amoxicillin orally and were closely followed up. Our results demonstrate that the overall substitution rate of amoxicillin was very low (<5%). Moreover, the frequency of

Table 2. Comparison of probable acute infection by atypical bacteria between children with non-severe CAP treated with oral amoxicillin with or without treatment failure at 2 and 5 days of treatment

	Treatment failure at 2 days				Cumulative failure at 5 days			
Acute infection by	yes	no	total	*P*	yes	no	total	*P*
M. pneumoniae								
yes	19 (11.7%)	67 (10.7%)	86	0.7	19 (11.2%)	65 (10.9%)	84	0.9
no	143	558	701		150	530	680	
total	162	625	787		169	595	764	
C. pneumoniae								
yes	12 (8.5%)	67 (11.3%)	79	0.3	12 (8.1%)	66 (11.6%)	78	0.2
no	130	524	654		136	505	641	
total	142	591	733		148	571	719	
C. trachomatis								
yes	1 (16.7%)	2 (9.1%)	3	0.5	1 (16.7%)	2 (9.1%)	3	0.5
no	5	20	25		5	20	25	
total	6	22	28		6	22	28	
One of the three bacteria								
yes	26 (18.4%)	121 (20.5%)	147	0.6	26 (17.7%)	119 (20.9%)	145	0.4
no	115	469	584		121	451	572	
total	141	590	731		147	570	717	

Results are given as absolute number (%).

Table 3. Comparison of probable acute infection by atypical bacteria between children with non-severe CAP treated with oral amoxicillin with or without radiologically diagnosed pneumonia at the 14 day follow-up visit

	Concordant radiologically diagnosed pneumonia			
Acute infection by	yes	no	Total	*P*
M. pneumoniae				
yes	8 (16.0)	75 (11.6)	83	0.3
no	42	574	616	
total	50	649	699	
C. pneumoniae				
yes	7 (14.9)	65 (10.4)	72	0.3
no	40	561	601	
total	47	626	673	
One of the two bacteria				
yes	13 (27.7)	124 (19.8)	137	0.2
no	34	502	536	
total	47	626	673	

Results are given as absolute number (%).
None of the cases with *C. trachomatis* acute infection had concordant radiologically diagnosed pneumonia.

amoxicillin substitution was similar among children with laboratory tests suggesting or ruling out acute infection by atypical bacteria. Moreover, although one-fifth of the patients had probable infection by one of the three studied atypical bacteria, no differences in atypical bacteria acute infection frequency were found when children with or without treatment failure were compared.

Several attempts have been made to address the question if acute infection by atypical bacteria requires empirical antibiotic treatment as the first-line option. In a retrospective multicentre cohort conducted in the USA, children hospitalized with CAP aged 1–4 years received either ceftriaxone alone or ceftriaxone plus macrolide; the results showed no significant difference in length of stay in the hospital alongside higher costs in the combination therapy group.[17] A similar study included hospitalized children with CAP, receiving either β-lactam monotherapy or β-lactam plus macrolide; no difference on readmission rate at 14 days after discharge was found.[18] In adults with non-severe CAP, the effectiveness of β-lactam antibiotics was compared with antibiotics active against atypical pathogens in a meta-analysis: equivalence was seen for *M. pneumoniae* and *C. pneumoniae* infection.[19] Herein, none of the changes to initial treatment that was carried out, due to failure, included an antibiotic with activity against atypical pathogens, suggesting that these subjects may have developed complications frequently seen with infection by pneumococcus or other typical bacteria. To the best of our knowledge, this is the first prospective cohort study in which a large sample of children aged <5 years, with non-severe CAP, received β-lactam monotherapy, had atypical pathogens acute infection investigated and were closely followed-up.

A recent rigorous systematic review and meta-analysis of the literature on the use of antibiotics to treat community-acquired lower respiratory infections secondary to *M. pneumoniae* among children considers the evidence insufficient to support or refute such treatments.[20] It is important to recall that patients with

Table 4. Comparison of amoxicillin substitution rate in children with non-severe CAP with or without probable atypical bacterial infection

	Acute infection by *M. pneumoniae*		
Antibiotic substitution	yes	no	*P*
yes	4 (4.8)	21 (3.2)	0.5
no	80	634	
total	84	655	
	Acute infection by *C. pneumoniae*		
Antibiotic substitution	yes	no	*P*
yes	2 (2.6)	18 (2.9)	1
no	75	608	
total	77	626	
	Acute infection by *M. pneumoniae* and/or *C. pneumoniae*		
Antibiotic substitution	yes	no	*P*
yes	5 (3.5)	15 (2.7)	0.6
no	139	544	
total	144	559	

Results are given as absolute number (%).

M. pneumoniae infections mostly recover spontaneously experiencing a self-limiting disease.[21] A minority of patients complain of persistent or progressive illness.[22] It has been estimated that 18% of children hospitalized with community-acquired lower respiratory tract infection with *M. pneumoniae* and/or *C. pneumoniae* acute infection present clinical failure in the absence of appropriate therapy.[7] On the other hand, the proportion of *M. pneumoniae* isolates carrying point mutations associated with macrolide resistance has increased and the development of such resistance occurs during macrolide treatment.[23] Additionally, it has been shown that more complications, with more extra-pulmonary alterations, occur in macrolide-resistant than in macrolide-susceptible *M. pneumoniae* pneumonia.[24] Thus, it is possible to infer from our results that not every child between 2 and 59 months of age, with non-severe CAP due to atypical bacteria, warrants specific antibiotic treatment as the first-line choice. In contrast, non-β-lactam antibiotics that treat these pathogens may be placed in the second-line option, if the β-lactam therapy fails.

Our results must be viewed with caution. The diagnosis of acute infection was based on serological tests. Following infection, IgM against *M. pneumoniae* may be detected after ∼1 week of illness, peaking at 3–6 weeks, followed by a gradual decline in children >6 months of age; however, IgM can sometimes persist for several weeks to months, or may not occur at all.[25] The longest median symptom among our patients was 5 days (IQR = 3–8 days), which was cough, and the mean interval between enrolment and the follow-up visit was 20±7 days [median (IQR) = 19 (16–22) days]. As a matter of fact, we opted to search for specific IgM against *M. pneumoniae* in serum samples collected at the follow-up visit to maximize the detection among delayed responders. Nonetheless, we could not rule out long persistent IgM, or false-negative IgM. Another option would have been to search for the presence of *M. pneumoniae* in nasopharyngeal samples by using PCR tests, which are inherently more sensitive tools and can detect *M. pneumoniae* earlier than serology.[25] In spite of that, it has recently been shown that *M. pneumoniae* is commonly present in the upper respiratory tract of asymptomatic children.[26] In a paediatric study, PCR detected *M. pneumoniae* in 64% of patients with acute asthma, 65% with refractory asthma and 56% of healthy controls.[27] Serologically diagnosed *C. pneumoniae* infections are shown to occur in children.[28] However, the use of serology alone may underestimate the incidence of *C. pneumoniae* infection.[29] As isolation of *C. pneumoniae* is cumbersome and PCR is not widely available, antibody testing using paired sera taken 4–8 weeks apart is recommended for diagnosis.[30] Diagnosis of *C. trachomatis* lung infections in infants by IgM serology is preferable to the isolation of the pathogen,[31] but the performance of PCR versus serology in a paediatric setting has not been evaluated. These figures suggest that the best strategy for convincing microbiological diagnosis requires a complex investigation, including the performance of serologic tests along with PCR. An additional limitation is that no additional testing was performed to identify viral–bacterial or bacterial–bacterial coinfection. On the other hand, the strengths of our work must be emphasized: the studied sample is a good representation of the patients routinely seen by doctors in daily practice, the sample was large, all procedures were standardized according to international standards and patients were closely followed-up, those being lost to follow-up were minimal (48 of 787: 6.1%). This last finding was because when a child did not come back on the initially scheduled date (14 days after recruitment), the paediatrician called the caregiver to schedule a new date and avoid losing the follow-up. That is why the median (IQR) interval between

recruitment and the 14 day follow-up visit was 19 (16–22) days. The clinical failure criteria were defined *a priori* based on standardized criteria used in CAP clinical trials. However, as all of our patients were followed-up by trained paediatricians who were members of the research team, the decision on amoxicillin substitution was made by them when they realized if the patient had worsened, or had not improved after at least 48 h of treatment, or had even fallen sick again after improvement had been seen. When we analysed the difference between the rates of treatment failure by the standardized criteria and of amoxicillin substitution, it was possible to observe that a patient could have fulfilled the treatment failure standardized criteria by presenting at least one item of the criteria (e.g. persistence of fever) but the paediatrician observed that the same patient improved in other symptoms and signs (e.g. resolution of tachypnoea) and therefore decided to keep the initial treatment. By waiting for longer, the child had resolution of fever and then amoxicillin was not substituted but the case was considered as treatment failure based on the standardized criteria. Based on this detailed follow-up and careful management of the patients, the cases with amoxicillin substitution were the ones with real treatment failure. Despite the uncertainty of an acute atypical bacterial infection diagnosis, this paper adds evidence on the absence of necessity to give empirical macrolides to every child with non-severe CAP.

In conclusion, it is not necessary to give an empirical non-β-lactam antibiotic as a first-line option to treat every child between 2 and 59 months of age with non-severe CAP.

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Transparency declarations

None to declare.

Author contributions

C. M. N.-C. conceptualized and designed the study, carried out the analyses and drafted the initial manuscript. G. X.-S. took part in data collection and analyses. A.-L. V.-B. and M.-S. H. F. supervised data collection and followed-up the patients. A. B. performed the investigation about *M. pneumoniae* acute infection. M. P. performed the investigation about *C. pneumoniae* and *C. trachomatis* infection. All members of the PNEUMOPAC-Efficacy Study Group took part in the recruitment and follow-up procedures, as well as in the discussion of the implementation and findings. All authors, including O. R., contributed to the interpretation of the findings, reviewed and revised the manuscript and approved the final version. C. M. N.-C. is the principal investigator for the study and the overall guarantor.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

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