HHS Public Access

Author manuscript

Paediatr Int Child Health. Author manuscript; available in PMC 2022 November 08.

Published in final edited form as:

Paediatr Int Child Health. 2021 August ; 41(3): 188–198. doi:10.1080/20469047.2021.1980698.

Prevalence, risk factors and outcome in Ugandan children infected with *Mycoplasma pneumoniae*: a prospective study

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Abstract

Background: Atypical bacteria cause 10–40% of all childhood community-acquired pneumonia and severe disease in children under 5 years of age. Data on the burden of atypical pneumonia in sub-Saharan Africa are limited.

Aim: To determine the prevalence, associated factors, and outcome of *Mycoplasma pneumoniae* infection in children presenting with respiratory symptoms at Mulago National Referral Hospital, Kampala.

Methods: Children aged 2 months to 12 years who presented with cough and/or difficult breathing and fast breathing were recruited. A clinical history and physical examination were undertaken. Blood samples were taken at enrolment (Day 0) and on Day 21 to determine the presence of *Mycoplasma pneumoniae* IgM antibodies, and induced sputum for DNA-PCR. Admitted participants were followed for a maximum of 7 days or until discharge or death, whichever came first.

Results: A total of 385 children were enrolled, and, of these, 368 (95.6%) were <5 years of age and the other 17 (4.4%) 5–12 years. Overall, 60/385 (15.6%) participants tested positive for *M. pneumoniae* IgM and/or DNA-PCR. Of these, 56/60 (93.3%) were <5 years of age. Wheezing was present in 21/60 (35.0%) of the children with atypical pneumonia (*Mycoplasma pneumonia*) and in 128/325 (39.4%) of those with typical pneumonia. The factors associated with *M. pneumonia* were female sex (AOR 1.94, 95% CI 1.22–3.08, $p<0.001$), age ≥12 months (AOR 2.73, 95% CI 1.53–4.87, $p=0.01$) and a history of prematurity (AOR 2.07, 95% CI 1.23–3.49, $p=0.01$). The overall mortality was 17/352 (4.8%) and, of these, 4/17 (23.5%) had *M. pneumonia*.

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Authors' contributions

RN, GN, FB and JKT participated in the conception and design of the study. RN coordinated the study implementation. IN managed and analysed the data. RN and IN drafted the manuscript. All authors reviewed and approved the final manuscript

Conflict of interest: None.

Conclusion: In Uganda, *M. pneumonia* is common in children <5 years of age, especially females above 2 years, and in those with a history of prematurity. It presents with severe symptoms requiring hospitalisation. The results highlight the importance of considering atypical bacteria in under-5s who present with symptoms of pneumonia.

Keywords

Mycoplasma pneumonia ; atypical pneumonia; prevalence; outcome

Introduction

Pneumonia is the leading cause of child morbidity and mortality, particularly in low- and middle-income countries (LMICs). It is responsible for 17% of the annual 5 million deaths of children <5 years of age and is the leading infectious cause of death in this age group [1,2]. In 2018, an estimated 802,000 children died of pneumonia. In most cases, especially in low-income settings where diagnostics such as radiological and laboratory investigations are limited, children are treated empirically with antibiotics against common bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae*, Klebsiella species and *Staphylococcus aureus* [1–3]. Although there has been some decline in pneumonia-associated morbidity and mortality following strategic interventions such as case management strategies, vaccines, especially pneumococcal conjugate vaccine (PCV) and *H. influenzae* type b (Hib), the successful prevention of mother-to-child transmission of human immunodeficiency virus (HIV) programmes and antiretroviral therapy (ART), the number of deaths from pneumonia remains unacceptably high [2,4]. While this may be related to access to and the quality of interventions, delayed care-seeking and viral pathogens [5–9], the contribution of atypical bacteria to pneumonia-associated childhood morbidity and mortality may be significant. In many low-income countries such as Uganda, its magnitude has not been investigated.

Previously, atypical pneumonia was thought to be a mild disease and more prevalent in schoolchildren. Recently, however, several studies have indicated a significant burden of atypical pneumonia in children <5 years of age, particularly in LMICs [10–12]. Studies in Latin America, the Caribbean, North Africa, and Asia have estimated that the prevalence of atypical pneumonia is 10–30% of total pneumonia cases in children, and *M. pneumoniae* is the most common causative organism [10–14]. In these studies, most affected children were <5 years of age. It was also observed that the disease was more severe in the younger age group (<5 years) than in older children. In a tertiary-level hospital study in Vietnam of 722 children aged 1–15 years with pneumonia symptoms, atypical organisms were isolated in 215 (29.8%), 97 (45.1%) of whom had severe disease, and 85 of the 97 (87.6%) were <5 years of age [10]. In another population-based survey of 3489 young children in Thailand, up to 15% had severe atypical pneumonia [15], and only 15% of those had received a prescription for macrolide antibiotics which is the recommended treatment. This may be an indicator of clinicians' low index of suspicion of atypical pneumonia which might be related to the scarcity of information on the burden of atypical organisms in children with pneumonia. In addition, children with atypical pneumonia may have radiographical findings similar to those of typical pneumonia [16]. This indicates that, even with chest radiographs being the current gold standard for diagnosing typical bacterial pneumonia, children with

atypical pneumonia may be missed or misdiagnosed as typical pneumonia and therefore do not receive the correct treatment with macrolide antibiotics.

The main risk factors for childhood pneumonia include malnutrition, immunosuppression owing to HIV infection, exposure to HIV, tobacco smoke and air pollution, lack of exclusive breastfeeding and immunisation, and young age [1,2,17]. In addition to these risk factors, atypical pneumonia is also more common in children with sickle cell anaemia (SCA), cardiac disease and asthma [18–22]. A study in India of 90 HIV-infected children with pneumonia showed that 32% had atypical organisms [23]. Studies have indicated that children with SCA are at high risk of atypical pneumonia which usually manifests as acute chest syndrome (ACS) which has been associated with an adverse outcome [18,21,24]. In Uganda, a study in children with SCA and ACS showed that 59.2% had *Chlamydia pneumoniae* in sputum [25]. Uganda has a high burden of SCA and pneumonia [26] and, therefore, the role of atypical pneumonia in this vulnerable population needs to be further explored.

Hitherto, childhood pneumonia in Uganda has been caused largely by *H. influenza* type b, *S. pneumoniae* and *S. aureus* [27,28]. However, vaccination against *H. influenza* type b (Hib vaccine) and *S. pneumoniae* (PCV) was introduced in the national programme for routine immunisation in 2002 and 2014, respectively. The current coverage for Hib is 93% while that for PCV is 92% [29]. It is therefore anticipated that with such high coverage the prevalence of pneumonia owing to these two organisms will decline significantly. Consequently, the role of atypical organisms such as *M. pneumoniae* and *C. pneumoniae* will become more significant and apparent.

This study aimed to determine the prevalence and describe the associated factors and outcome in children with atypical pneumonia in a tertiary-care hospital in Uganda.

Subjects and methods

Design, setting and population

This prospective study was undertaken in the paediatric Acute Care Unit (ACU) of Mulago Hospital which is a national referral hospital in Uganda. It is also a teaching hospital for Makerere University's College of Health Sciences. The ACU is a paediatric emergency unit which receives patients aged 1 day to 12 years referred from private and public health units in Kampala Capital City Authority and other districts. Patients typically have acute symptoms such as fever, cough, difficult breathing, wheezing with/without general danger signs of convulsions, severe vomiting, inability to feed, lethargy and unconsciousness. Children with chronic diseases such as renal, cardiac, or metabolic diseases with complications such as severe anaemia, cardiac failure, renal failure, and diabetic ketoacidosis are also seen in the ACU. Although Mulago Hospital is primarily a national referral hospital, an estimated 50% of carers use it as the first point of care for their sick children. The average number of children seen daily in the ACU is 50 and an estimated 25% present with cough and/or difficult breathing. Mulago Hospital was selected for this study because of its proximity to facilities which can undertake the laboratory investigations required.

Sampling and eligibility criteria

The convenience method of sampling was used. Eligible children were enrolled consecutively until the desired sample size was achieved. In line with the World Health Organization (WHO) definition of pneumonia [30], children aged 2–59 months who presented to the ACU with cough, with/without difficult breathing and fast breathing with/without chest indrawing were eligible. Children >5 years were eligible for inclusion if they had a cough with/without sputum and fast breathing (>30 breaths/min) with/without chest indrawing [3]. Children with severe anaemia were excluded because the signs and symptoms of difficult breathing, fast breathing and respiratory distress were likely to be secondary to heart failure. Severe anaemia was considered if the child's palms and soles were very pale and haemoglobin was ≤5 g/dl.

Recruitment of study participants

Children arriving at the ACU were triaged, and those assessed as severe respiratory disease were identified and managed in accordance with the emergency triage assessment and treatment guidelines [31]. Children aged 2 months to 12 years with cough and/or difficult breathing were identified and those fulfilling the eligibility criteria were recorded. Their carers were then approached for written informed consent to participation in the study.

A questionnaire was then administered by the study nurse, followed by physical examination by the study doctor who was also responsible for treating the children in accordance with the standard Uganda guidelines for management of pneumonia [3,30]. Nutrition was assessed according to WHO guidelines on the management of children with severe malnutrition [32]. The arterial peripheral oxygen saturation (SpO_2) in room air was measured in all participants. Children in whom it was <92% were given oxygen by mask or nasal prongs.

Blood and sputum collection

Six millilitres of venous blood were drawn from the cubital vein or dorsum of the hand using a BD™ blood collection set in two aliquots: 2 ml for complete blood cell count (CBC) and 4 ml for *M. pneumoniae* IgM testing. In addition, children of unknown HIV status were tested for HIV. On Day 21, another blood sample was collected during the follow-up visit after admission for a repeat serological *M. pneumoniae* IgM test.

Sputum was induced to obtain samples for polymerase chain reaction (PCR) analysis for *M. pneumoniae*. All study participants were first screened for suitability to undergo sputum induction (SI). Specifically, children with hypoxaemia (SpO_2 <90%), thrombocytopenia and risk factors for hypokalaemia such as diarrhoea and vomiting did not undergo SI until the symptoms had resolved. Children who were suitable for SI were first pre-medicated with nebulised salbutamol to prevent the bronchoconstriction usually associated with hypertonic saline nebulisation. They were then nebulised with 5 ml of hypertonic (2.5%) saline solution which helps to mobilise and soften the sputum and moves it up the airway for easy expectoration or extraction [33]. After nebulisation, a suction catheter directly connected to a sputum trap was introduced into the nasopharynx and suction undertaken using a foot-operated machine. Infection control procedures were employed such as wearing a mask, using sterile equipment, and maintaining sterility. The room in which SI was undertaken

was well ventilated to reduce the risk of transmission of infection, particularly tuberculosis. Older children (>5 years) were encouraged to cough into a sputum container. The SI procedure was successful in 92.2% (357/387) of participants.

Laboratory procedures

The blood for IgM serological tests was immediately transferred into a cold box at 4°C. The IgM used was Demeditec *Mycoplasma pneumoniae* IgM ELISA DEMYCM0350 (Demeditec Diagnostics GmbH, Germany). The sample for CBC was kept at room temperature until transferral to the laboratory. All samples reached the laboratory within 8 hours of collection. The Coulter counter method was used to measure the total and differential white cell count. The sputum quality was assessed both macroscopically to determine whether it was saliva and by the Gram stain method. Gram stain quantified the number of organisms in the sputum, and all samples with >10 squamous epithelial cells per low power field were considered to be of poor quality. The PCR results from such samples were not analysed for *M. pneumoniae*. In these participants, only the results of the IgM for *M. pneumoniae* were considered.

Serological tests for M. pneumonia.—The Mycoplasma IgM Test System is a qualitative detection of IgM antibodies to *M. pneumoniae* in human sera. IgM ELISA testing was undertaken using the blood sample collected on enrolment (Day 0) and during the follow-up visit (Day 21).

PCR test.—The induced sputum was tested by PCR for *M. pneumoniae*. Specifically, the illumigene® Mycoplasma (Meridian Bioscience, USA) test was used to detect *M. pneumoniae* in the sputum. The illumigene Mycoplasma assay is a loop-mediated isothermal amplification (LAMP) assay that enables detection of *M. pneumoniae* in up to ten clinical specimens which can be tested simultaneously within an hour after the extracted DNA is set up in the incubator/reader. Blood and sputum samples were also bio-banked for future studies.

Interpretation of test results.—The test results from IgM ELISA and sputum PCR were interpreted as follows: ELISA IgM (Days 0 and 21) and PCR negative = no evidence of infection; ELISA IgM and PCR positive = acute infection; ELISA IgM negative on Day 0 but positive on Day 21, and PCR negative = acute infection; ELISA IgM negative (Days 0 and 21) but PCR positive = acute infection.

In this study, children who tested positive for *M. pneumoniae*, the most common atypical bacteria [10,11,14], were referred to as having atypical pneumonia. The rationale for this study was to highlight the importance of atypical bacterial organisms as a cause of pneumonia in children, because most pneumonia treatment guidelines focus on typical bacterial causes. However, owing to limited resources, it was only possible to test for *M. pneumoniae*.

Management of study participants

All participants were managed according to the Ugandan standard guidelines for pneumonia [3,30]. They were followed up until discharge to document the clinical outcome including duration of hospitalisation, normalisation of respiratory rate and peripheral oxygen saturation, and fever clearance. The study nurse assessed these twice a day.

Participants were followed up on Day 21 after enrolment when 2 ml of blood were drawn for the second IgM serological test. All participants were reviewed clinically, focusing on respiratory symptoms. Any other medical problems were also addressed.

Statistical analysis

Before data were collected, the case record forms (CRF) were pre-tested on 20 patients in the ACU with respiratory symptoms to check for understanding and completeness and were revised accordingly.

Data were collected using hard copy CRF. All completed CRF and other study records such as consent forms, study registers and test results were filed appropriately and locked in the study cabinets to which only the study team had access. Clinical care records such as results of CBC and HIV were available to the clinical care team. A copy of the results was also given to the carer. In addition, carers who tested positive for HIV infection underwent post-test counselling and were referred for care.

Data were checked regularly for quality and completeness by the principal investigator, and any issues arising were addressed immediately or during the weekly research team meetings.

Data were entered into Epidata version 3.1 and exported to Stata version 13.0. for cleaning and analysis. Descriptive statistics were used to analyse for the baseline, clinical and laboratory characteristics of the participants, and the results were expressed as proportions, means and medians, as appropriate. To determine the prevalence of atypical pneumonia in the study population, the number of participants with a positive PCR or IgM test on Days 0 or 21 was divided by the total number of participants, and the result were expressed as a proportion. To determine factors independently associated with atypical pneumonia, multivariable analysis was undertaken. A logistic regression model was built by including all factors with $p<0.2$ by bivariate analysis. Multi-collinearity and interaction of the predictor variables were also checked until the best fitting model was obtained; $p\leq0.05$ was considered statistically significant. Odds ratios and 95% confidence intervals (CI) are presented. Survival analysis was undertaken to compare the occurrence of specific events such as time to discharge and resolution of signs and symptoms in children with atypical pneumonia and in those with non-atypical pneumonia. A log rank test p-value of ≤0.05 was considered statistically significant. Children who died and those who were lost to follow-up were excluded.

Ethics

Ethics approval was granted by the Higher Degrees, Ethics and Research Committee (HDREC-Number 2017-033) of Makerere College of Health Sciences and the Uganda

National Council for Science and Technology (UNCST Number HS56ES). Informed written consent was given by the children's carers.

Results

Demographic characteristics of the study participants

A total of 387 participants were enrolled, two of whom were not included in the analysis because their sputum samples were of poor quality, and obtaining blood samples for ELISA failed; therefore, the presence or absence of *M. pneumoniae* could not be ascertained.

Of the 385 participants, 226 (58.9%) were male. The median (IQR) age was 13 months (7–24 months), 165 (42.9%) were infants (age <12 months) and only 17 (4.4%) were over 5 years of age. The majority (344/385, 89.4%) were from urban settings.

Prevalence of atypical pneumonia

The diagnosis of atypical pneumonia was based on any of the following: (i) a positive DNA-PCR test for *M. pneumoniae* in the sputum, (ii) high *M. pneumoniae* IgM titres at enrolment, and (iii) high *M. pneumoniae* IgM titres on Day 21 after enrolment. Based on the above criteria, 60/385 (15.6%) participants tested positive for *M. pneumoniae*. Of these, 56/60 (93.3%) were under 5 years of age. The median (IQR) age of the children with atypical pneumonia was 18 months (12–36) and in those with typical pneumonia it was 12 months (6–22).

Clinical and laboratory characteristics of the study participants

The clinical symptoms, findings on physical examination and laboratory characteristics were similar in the children with atypical and typical pneumonia (Table 1).

Co-morbidities

A total of 27 children had SCA, four of whom (14.8%) had *M. pneumonia*. Eight children had HIV infection, one of whom was diagnosed with *M. pneumonia*. Thirty-nine children were HIV-exposed and 7 (17.9%) of them had *M. pneumonia*. Up to 119/285 (30.9%) of all participants had a history of recurrent difficult breathing or wheezing, indicating a high likelihood of asthma syndrome. Regarding a history of wheezing, there was no statistically significant difference between the children with atypical (11/60) and typical pneumonia. The other symptoms usually used to assess for possible asthma in this age group such as night and/or early morning coughing and awakening also indicated that up to 50% of the children might have had asthma syndrome (Table 2).

Factors associated with M. pneumonia

The factors that were significantly associated with *M. pneumonia* were age (AOR 2.73, 95% CI 1.53–4.87, $p<0.001$), female sex (AOR 1.94, 95% CI 1.22–3.08, $p=0.01$) and a history of prematurity (AOR 2.07, 95% CI 1.23–3.49, $p=0.01$). Other factors investigated including nutritional status, HIV status, exclusive breastfeeding, exposure to tobacco smoke, SCA, chronic cough, asthma syndrome and immunisation status were not significantly associated with *M. pneumonia* (Table 3).

Outcome of children with M. pneumonia

The outcomes of particular interest included discharge, complications, admission to the intensive care unit and death. The children were followed up on Day 21 after enrolment to document any symptoms which may have persisted or recurred. There was no statistically significant difference in outcome between the children with atypical and non-atypical pneumonia. The overall mortality was 17/352 (4.8%). Of the 17 children who died, 4 (23.5%) had *M. pneumonia* (Table 4).

All children who were admitted were followed up to document duration of hospitalisation, time to resolution of fever, chest indrawing and normalisation of respiratory rate and peripheral oxygen saturation. There was no statistically significant difference in the above factors between children with atypical pneumonia and those with typical pneumonia (see online-only supplementary Figures 1–4).

Discussion

The aim of the study was to determine the prevalence of *M. pneumoniae* in children with respiratory symptoms presenting at Mulago National Referral Hospital. In addition, the associated factors and immediate clinical outcome are described.

Overall, 60 of 385 (15.6%) children tested positive for *M. pneumoniae* by PCR or IgM. The findings also showed that female sex, a history of prematurity and age were associated with an increased risk of *M. pneumonia*. The overall mortality rate was 4.8%, and 94% of the children recovered without complications. There was no statistically significant difference in time to resolution of key signs and symptoms of pneumonia such as fever, normalisation of respiratory rate and peripheral oxygen saturation and resolution of chest indrawing between the children with atypical pneumonia and those with typical pneumonia.

This is the first study in Uganda to document the burden of atypical pneumonia in children presenting to a general paediatric unit with respiratory symptoms. The prevalence of 15.6% is similar to that in studies in Vietnam, Egypt, Latin America, and the Caribbean [10,11,13]. In Vietnam, the prevalence of atypical pneumonia in children with acute respiratory symptoms was 29.8% and in Egypt the prevalence was around 11.1% [10,11]. Treatment guidelines for pneumonia in most LMIC focus on typical organisms as the cause of symptoms, and the antibiotics given empirically to children with pneumonia symptoms target organisms such as *S. pneumoniae, H. influenzae, S. aureus* and Klebsiella species [3,30]. There is no explicit guidance on the treatment of children with pneumonia caused by atypical organisms. This may be related to the fact that atypical pneumonia was thought to be a mild disease (‘walking pneumonia’) in school-age children. However, studies have shown that atypical organisms are associated with pneumonia in children <5 years of age and can cause severe disease in this age group [10]. The findings of this study highlight the importance of atypical organisms as a cause of severe pneumonia, and that some children are not treated with macrolide antibiotics, which increases the risk of complications and even death, or repeated hospital visits because of inappropriate treatment. The study was undertaken in a tertiary-care hospital where most children present with severe disease. It is not clear if the situation is the same in primary-care settings where most children

present with non-severe pneumonia. Therefore, further studies are recommended to generate evidence to guide the need for review of the current guidelines on the management of childhood pneumonia.

Clinical and laboratory characteristics of children with atypical pneumonia

There were many similarities in the clinical and laboratory characteristics of atypical and typical pneumonia. This indicates that, as with typical organisms, atypical organisms induce acute and severe symptoms with the potential to cause complications and even death. Currently, it is not possible to distinguish atypical from typical pneumonia based on symptoms or severity. Therefore, the need for point-of-care diagnostics is crucial in order to provide the appropriate antibiotics.

Another important finding was the presence of symptoms suggesting asthma syndrome in up to 30% of the children, whether atypical or typical pneumonia. A study in Denmark also demonstrated that children with atypical pneumonia commonly presented with asthma-like symptoms [34]. This resonates with findings in earlier studies in which a significant proportion (41%) of children with pneumonia symptoms had asthma syndrome [35]. Such cases are usually treated as pneumonia with antibiotics, and this usually results in repeated hospital visits. In addition, it is recognised that atypical organisms are a common cause of asthma exacerbation in children [20,22]. This underscores the importance of continuously considering the possibility of asthma syndrome in children who present with respiratory symptoms.

Risk factors for atypical pneumonia

In this study, the independent predictors of atypical pneumonia were age >12 months, female sex, and prematurity. It is not clear why females are more likely to have atypical pneumonia. Generally, premature children are at greater risk of pneumonia [6], but it is not clear why prematurity was associated with an increased risk of atypical pneumonia, and this needs to be explored further. Similar studies of risk factors for severe atypical pneumonia found that it was more likely to occur in infants, in whom it was severe [10]. Other risk factors for atypical pneumonia include SCA in which it causes acute chest syndrome, asthma which is associated with exacerbation, and HIV infection [18,20,21,23]. However, in this study, these factors were not found to be statistically significant, probably owing to the small number of children with such factors.

Outcome in children with atypical pneumonia

The overall mortality rate was 4.8%, and, of these, 4/17 (23.5%) had atypical pneumonia. The majority (94%) improved without complications, but hospitalisation was prolonged (>4 days) in many (50%). Furthermore, there was no statistically significant difference in resolution of symptoms between the children with atypical and typical pneumonia. These findings indicate that atypical pneumonia runs a clinical course similar to that in children who do not have atypical pneumonia. The reasons are unclear but might relate to the type of treatment given: some might have received macrolide antibiotics against the atypical organisms. However, treatment details were not systematically recorded to aid meaningful analysis.

Limitations

Co-infection with viruses and typical bacteria is common and may be responsible for the severe symptoms in children with atypical pneumonia. It was not possible to test for viruses, other atypical organisms and typical bacteria in this study population. However, some studies have shown that even children in whom atypical organisms are the sole cause of the pneumonia symptoms can have severe disease [10]. In addition, most studies have demonstrated that the most common atypical organism in children with pneumonia is *M. pneumoniae* [10,11,14]. It is therefore prudent to consider the possibility of these organisms in children with severe pneumonia.

Although random sampling minimises bias, it was not possible in this study because access to the participants depended on their attendance at the ACU. However, studies of sampling methods have indicated that consecutive screening and enrolment are feasible and offer representative samples in clinical studies [36]. Therefore, the assumption was that the sampled children were representative of those seen at the ACU at Mulago National Referral Hospital.

Conclusion

Atypical bacterial organisms cause significant morbidity in children under 5 years with acute respiratory symptoms. Female sex, a history of prematurity and age ≥12 months were significantly associated with atypical pneumonia. The clinical presentation and outcome in children with atypical pneumonia are similar to those in children with typical pneumonia, making it challenging to diagnose solely on the basis of clinical features. Up to one-third of the participants had symptoms such as recurrent difficult breathing or wheezing and night coughs, indicating the high likelihood of asthma syndrome. Studies on point-of-care diagnostics for pneumonia and asthma syndrome are urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We are grateful to the children and their carers and to the research assistants. This work was supported by Grant Number D43TW010132, supported by the Office of the Director, National Institutes Of Health (OD), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Neurological Disorders and Stroke (NINDS), National Heart, Lung and Blood Institute (NHLBI), Fogarty International Center (FIC), National Institute on Minority Health and Health Disparities (NIMHD). The contents of the article are solely the responsibility of the authors and do not necessarily represent the official views of the supporting offices.

Data availability:

The data that support the results of the study are available from the corresponding author upon reasonable request.

Abbreviations:

ACU	Acute Care Unit

ACS	acute chest syndrome
ART	antiretroviral therapy
CBC	complete blood count
CRF	case record form
ELISA	enzyme-linked immunosorbent assay
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
IgM	immunoglobulin M
IMCI	integrated management of childhood illnesses
LMIC	low- and middle-income countries
M. pneumonia	*Mycoplasma pneumonia* (pneumonia caused by *Mycoplasma. pneumoniae* bacteria)
PCV	pneumococcal conjugate vaccine
PCR	polymerase chain reaction
SCA	sickle cell anaemia
SI	sputum induction
SpO_2	peripheral arterial oxygen saturation
UNCST	Uganda National Council for Science and Technology
WHO	World Health Organization

References

1. Save the Children. Fighting for breath: a call to action on childhood pneumonia. 2017. Available from: https://resourcecentre.savethechildren.net/library/fighting-breath-call-action-childhood-pneumonia
2. Save the Children. Every Child's Right to Survive: An Agenda to End Pneumonia Deaths. 2019. Available from: https://www.unicef.org/reports/every-childs-right-survive-pneumonia-2020)
3. Uganda Clinical Guidelines: National Guidelines for Managament of Common Conditions. 2018. Ministry of Health, Kampala.
4. McCollum ED, McCollum B, Nambiar R, et al. Impact of the 13-valent pneumococcal conjugate vaccine on clinical and hypoxemic childhood pneumonia over three years in Central Malawi: an observational study. PLoS One. 2017;12:e0168209. [PubMed: 28052071]
5. Bhuiyan MU, Snelling TL, West R, et al. The contribution of viruses and bacteria to community-acquired pneumonia in vaccinated children: a case-control study. Thorax. 2019;74:261–269. [PubMed: 30337417]
6. Colin AA, McEvoy C, Castile RG. Respiratory morbidity and lung function in preterm infants of 32 to 36 weeks' gestational age. Pediatrics. 2010;126:115–128. [PubMed: 20530073]

7. Ferdous F, Ahmed S, Das SK, et al. Pneumonia mortality and healthcare utilization in young children in rural Bangladesh: a prospective verbal autopsy study. Trop Med Health. 2018;46:17. [PubMed: 29875615]
8. Anaba U, Hutchison PL, Abegunde D, et al. Pneumonia-related ideations, care-seeking, and treatment behaviors among children under 2 years with pneumonia symptoms in northwestern Nigeria. Pediatr Pulmonol. 2020;55:S91–S103. [PubMed: 31990144]
9. O'Brien KL, Levine OS, Knoll MD, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet. 2019;394:757–779. [PubMed: 31257127]
10. Huong Ple T, Hien PT, Lan NT, et al. First report on prevalence and risk factors of severe atypical pneumonia in Vietnamese children aged 1–15 years. BMC Public Health. 2014;14:1304. [PubMed: 25524126]
11. Grassi T, Mancini F, Ciervo A, et al. Chlamydophila pneumoniae, Mycoplasma pneumoniae, and influenza in children with respiratory infections in Alexandria, Egypt. J Infect Dev Ctries. 2014;8:379–383. [PubMed: 24619271]
12. Weber MW, Gopalakrishna G, Awomoyi A, et al. The role of Chlamydia pneumoniae in acute respiratory tract infections in young children in The Gambia, West Africa. Ann Trop Paediatr. 2006;26:87–94. [PubMed: 16709325]
13. Gentile A, Bardach A, Ciapponi A, et al. Epidemiology of community-acquired pneumonia in children of Latin America and the Caribbean: a systematic review and meta-analysis. Int J Infect Dis. 2012;16:e5–e15. [PubMed: 22056731]
14. Williams DJ, Shah SS. Community-acquired pneumonia in the conjugate vaccine era. J Pediatr Infect Dis Soc. 2012;1:314–328.
15. Phares CR, Wangroongsarb P, Chantra S, et al. Epidemiology of severe pneumonia caused by Legionella longbeachae, Mycoplasma pneumoniae, and Chlamydia pneumoniae: 1-year, population-based surveillance for severe pneumonia in Thailand. Clin Infect Dis. 2007;45:e147–e155. [PubMed: 18190309]
16. Cho YJ, Han MS, Kim WS, et al. Correlation between chest radiographic findings and clinical features in hospitalized children with Mycoplasma pneumoniae pneumonia. PLoS One. 2019;14:e0219463. [PubMed: 31461462]
17. Le Roux DM, Zar HJ. Community-acquired pneumonia in children – a changing spectrum of disease. Pediatr Radiol. 2017;47:1392–1398. [PubMed: 29043417]
18. Dean D, Neumayr DL, Kelly DM, et al. Chlamydia pneumoniae and acute chest syndrome in patients with sickle cell disease. J Pediatr Hematol Oncol. 2003;25:46–55. [PubMed: 12544773]
19. Hassan J, Irwin F, Dooley S, et al. Mycoplasma pneumoniae infection in a pediatric population: analysis of soluble immune markers as risk factors for asthma. Hum Immunol. 2008;69:851–855. [PubMed: 18835573]
20. Johnston SL, Martin RJ. Chlamydophila pneumoniae and Mycoplasma pneumoniae: a role in asthma pathogenesis? Am J Respir Crit Care Med. 2005;172:1078–1089. [PubMed: 15961690]
21. Neumayr LE, Lennetteet D, Kelly D, et al. Mycoplasma disease and acute chest syndrome in sickle cell disease. Pediatrics. 2003;112:87–95. [PubMed: 12837872]
22. Shin JE, Cheon BR, Shim JW, et al. Increased risk of refractory Mycoplasma pneumoniae pneumonia in children with atopic sensitization and asthma. Korean J Pediatr. 2014;57:271–277. [PubMed: 25076972]
23. Nadagir SD, Kaleem Bahadur A, Anantappa Shepur T. Prevalence of Mycoplasma pneumoniae among HIV infected children. Indian J Pediatr. 2011;78:430–434. [PubMed: 21161445]
24. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. N Engl J Med. 2000;342:1855–65. [PubMed: 10861320]
25. Ochaya O, Hume H, Bugeza S, et al. ACS in children with sickle cell anaemia in Uganda: prevalence, presentation and aetiology. Br J Haematol. 2018;183:289–297. [PubMed: 30125958]
26. Ndeezi G, Hume H, Bugeza S, et al. Burden of sickle cell trait and disease in the Uganda Sickle Surveillance Study (US3): a cross-sectional study. Lancet Glob Health. 2016;4:e195–e200. [PubMed: 26833239]

27. Nantanda R, Hildenwall H, Peterson S, et al. Bacterial aetiology and outcome in children with severe pneumonia in Uganda. Ann Trop Paediatr. 2008;28:253–260. [PubMed: 19021940]
28. Srinivasan MG, Ndeezi G, Mboijana CK, et al. Zinc adjunct therapy reduces case fatality in severe childhood pneumonia: a randomized double blind placebo-controlled trial. BMC Med. 2012;10:14. [PubMed: 22316073]
29. World Health Organizatin, UNICEF. Immunization coverage in Uganda. 2020. Available from: https://www.who.int/immunization/monitoring_surveillance/data/uga.pdf
30. World Health Organization. Pocket Book for Hospital Care of Children: Guidelines for the Management of Common Childhood Illnesses. Geneva: WHO, 2013.
31. World Health Organization. Updated Guidelines: Paediatric Emergency Triage, Assessment and Treatment. Geneva. WHO. 2016.
32. Ministry of Health, Kampala. Integrated Management of Acute Malnutrition Guidelines. 2010.
33. Zar HJ, Tannenbaum E, Hanslo D, et al. Sputum induction as a diagnostic tool for community-acquired pneumonia in infants and young children from a high HIV prevalence area. Pediatr Pulmonol. 2003;36:58–62. [PubMed: 12772225]
34. Sondergaard MJ, Friis MB, Hansen DS, et al. Clinical manifestations in infants and children with Mycoplasma pneumoniae infection. PLoS One. 2018;13:e0195288. [PubMed: 29698412]
35. Nantanda R, Tumwine JK, Ndeezi G, et al. Asthma and pneumonia among children less than five years with acute respiratory symptoms in Mulago Hospital, Uganda: evidence of under-diagnosis of asthma. PLoS One. 2013;8:e81562. [PubMed: 24312321]
36. Bjorn M, Brendstrup C, Karlsen S, et al. Consecutive screening and enrollment in clinical trials: the way to representative patient samples? J Card Fail. 1998;4:225–230. [PubMed: 9754593]

Table 1.

Clinical and laboratory characteristics of the 385 study participants.

Variable		Atypical pneumonia *n* (%)	Typical pneumonia *n* (%)	Overall *n* (%)
Acute symptoms				
Cough	No	4 (6.7)	19 (5.8)	23 (6.0)
	Yes	56 (93.3)	306 (94.2)	362 (94.0)
Characteristic of cough	Dry cough	29 (50.9)	153 (50.0)	182 (50.1)
	Wet cough	28 (49.1)	153 (50.0)	181 (49.9)
Difficult breathing	No	7 (11.7)	27 (8.3)	34 (8.8)
	Yes	53 (88.3)	298 (91.7)	351 (91.2)
Wheezing	No	39 (65.0)	197 (60.6)	236 (61.3)
	Yes	21 (35.0)	128 (39.4)	149 (38.7)
Fever	No	13 (21.7)	64 (19.7)	77 (20.0)
	Yes	47 (78.3)	261 (80.3)	308 (80.0)
Vomiting	No	50 (83.3)	227 (69.9)	277 (71.9)
	Yes	10 (16.7)	98 (30.1)	108 (28.1)
Diarrhoea	Yes	48 (80.0)	233 (71.9)	282 (73.2)
	No	12 (20.0)	91 (28.1)	103 (26.8)
Axillary temperature (°C)	<37.5	34 (56.7)	159 (49.2)	193 (50.4)
	≥37.5	26 (43.3)	164 (50.8)	190 (49.6)
Peripheral oxygen saturation	<90%	19 (32.2)	120 (37.0)	139 (36.3)
	≥90%	40 (67.8)	204 (63.0)	244 (63.7)
Nutritional status	Normal	47 (82.4)	249 (80.1)	296 (80.4)
	Moderate malnutrition	5 (8.8)	35 (11.2)	40 (10.9)
	Severe malnutrition	5 (8.8)	27 (8.7)	32 (8.7)
Chest indrawing	No	21 (35.0)	114 (35.1)	135 (35.1)
	Yes	39 (65.0)	211 (64.9)	250 (64.9)
Auscultatory wheeze	No	47 (78.3)	258 (79.4)	305 (79.2)
	Yes	13 (21.7)	67 (20.6)	80 (20.8)
Crackles	No	36 (60.0)	159 (48.9)	195 (50.6)
	Yes	24 (40.0)	166 (51.1)	190 (49.4)
Laboratory characteristics				
Total white cell count (NR 4.0–10×10^3/L)	Normal	17 (33.3)	99 (37.1)	116 (36.5)
	High	34 (66.7)	163 (61.0)	197 (61.9)
	Low	0 (0.0)	5 (1.9)	5 (1.6)
Neutrophil count (NR 2.0–8.0×10^3/L)	Normal	31 (60.8)	168 (62.2)	199 (62.0)
	High	19 (37.2)	84 (31.1)	103 (32.1)
	Low	1 (2.0)	18 (6.7)	19 (5.9)
Lymphocytes (NR 0.8–7.0×10^3/L)	Normal	41 (80.4)	209 (77.4)	250 (77.9)
	High	10 (19.6)	61 (22.6)	71 (22.1)
HIV serology	Negative	59 (98.3)	318 (97.5)	377 (97.9)

Variable		Atypical pneumonia *n* (%)	Typical pneumonia *n* (%)	Overall *n* (%)
	Positive	1 (1.7)	7(2.5)	8 (2.1)

NR, normal range.

Table 2.

Asthma symptoms in the 385 study participants.

Variable		Atypical pneumonia *n* (%)	Typical pneumonia *n* (%)	Overall *n* (%)
Recurrent episodes of:				
Cough	No	9 (15.0)	83 (25.5)	92 (23.9)
	Yes	51 (85.0)	242 (74.5)	293 (76.1)
Difficult breathing	No	41 (63.8)	225 (69.2)	266 (69.1)
	Yes	19 (36.2)	100 (30.8)	119 (30.9)
Wheezing	No	49 (68.3)	273 (84.0)	322 (83.6)
	Yes	11 (31.7)	52 (16.0)	63 (16.4)
Does the child usually cough at night and/or in the early morning?	No	21 (35.6)	166 (51.4)	187 (49.0)
	Yes	38 (64.4)	157 (48.6)	195 (51.0)
Does the child usually have difficult breathing in the night and/or early morning?	No	45 (76.3)	250 (76.9)	295 (76.8)
	Yes	14 (23.7)	75 23.1)	89 (23.2)
Does the child usually wheeze in the night and/or early morning?	No	50 (83.3)	293 (90.2)	343 (89.1)
	Yes	10 (16.7)	32 (9.8)	42 (10.9)
Does the child sometimes wake up in the night with coughing?	No	39 (65.0)	210 (65.2)	249 (65.2)
	Yes	21 (35.0)	112 (34.8)	133 (34.8)
Child has/ever had allergies?	No	46 (83.6)	231 (82.8)	277 (82.9)
	Yes	9 (16.4)	48 (17.2)	57 (17.1)

Table 3.

Factors associated with atypical pneumonia in 385 children with acute respiratory symptoms in Mulago Hospital.

		Atypical pneumonia, *n* (%)					
Variable	**Yes**	**No**		**COR (95% CI)**	***p* value**	**AOR (95% CI)**	***p*-value**
Age, mths	2–12	14 (8.5)	151 (91.5)	1		1	
	12–59	42 (20.7)	161 (79.3)	2.44 (1.38–4.31)	<0.001	2.73 (1.53–4.87)	**<0.001**
	≥60	4 (23.5)	13 (76.5)	2.77 (1.03–7.49)	0.04	3.22 (1.17–8.84)	0.02
Sex	Male	27 (11.9)	199 (88.1)	1		1	
	Female	33 (20.8)	126 (79.2)	1.74 (1.09–2.77)	0.02	1.94 (1.22–3.08)	**<0.001**
Duration of cough, days	<7	48 (15.6)	259 (84.4)	1			
	≥7	12 (15.4)	66 (84.6)	0.98 (0.55–1.76)	0.96		
Nutritional status	Normal	47 (15.9)	249 (84.1)	1			
	Moderate malnutrition	5 (12.5)	35 (87.5)	0.78 (0.33–1.86)	0.59		
	Severe malnutrition	5 (15.6)	27 (84.4)	0.98 (0.42–2.30)	0.97		
HIV status	Negative	59 (15.6)	318 (84.4)	1			
	Positive	1 (12.5)	7 (87.5)	0.80 (0.13–5.08)	0.81		
History of exclusive breastfeeding for 6 months	No	14 (12.3)	100 (87.7)	1			
	Yes	44 (16.9)	217 (83.1)	1.37 (0.78–2.40)	0.27		
Prematurity	No	50 (14.4)	298 (85.6)	1			
	Yes	10 (29.4)	24 (70.6)	2.05 (1.14–3.66)	0.02	2.07 (1.23–3.49)	**<0.01**
Exposed to tobacco smoke	No	51 (14.7)	296 (85.3)	1			
	Yes	7 (20.0)	28 (80.0)	1.36 (0.67–2.77)	0.39		
Sickle cell anaemia	No	42 (15.2)	235 (84.8)	1			
	Yes	4 (14.8)	23 (85.2)	0.98 (0.38–2.52)	0.96		
Asthma syndrome	No	46 (14.4)	274 (85.6)	1			
	Yes	14 (21.5)	51 (78.5)	1.50 (0.88–2.56)	0.13		
Immunisation status Received PCV1	No	5 (14.3)	30 (85.7)	1			
	Yes	55 (15.9)	290 (84.1)	1.12 (0.48–2.61)	0.8		
Received pentavalent 3	No	9 (11.0)	73 (89.0)	1			
	Yes	50 (16.9)	246 (83.1)	1.54 (0.79–3.00)	0.20		
Received measles vaccine	No	16 (9.9)	146 (90.1)	1			

		Atypical pneumonia, *n* (%)					
Variable	**Yes**	**No**		**COR (95% CI)**	***p* value**	**AOR (95% CI)**	***p*-value**
	Yes	43 (20.4)	168 (79.6)	2.06 (1.21–3.53)	**0.01**		

AOR, adjusted odds ratio.

p-values in bold are statistically significant.

Table 4.

Outcome in 385 children with atypical and typical pneumonia.

Outcome		Atypical pneumonia *n* (%)	Typical pneumonia *n* (%)	Overall *n* (%)	*p*-value[a]
Clinical improvement	No	4 (8.0)	17 (5.6)	21 (6.0)	0.35
	Yes	46 (92.0)	284 (94.4)	330 (94.0)	
Overall complications	No	50 (100.0)	294 (98.0)	344 (98.3)	0.39
	Yes	0	6 (2.0)	6 (1.7)	
ICU care	No	48 (96.0)	294 (97.7)	342 (97.4)	0.37
	Yes	2 (4.0)	7 (2.3)	9 (2.6)	
Change of treatment	No	50 (100.0)	292 (97.0)	342 (97.4)	0.25
	Yes	0	9 (3.0)	9 (2.6)	
Hospitalisation ≥4 days	No	25 (50.0)	150 (49.8)	175 (49.9)	0.55
	Yes	25 (50.0)	151 (50.2)	176 (50.1)	
Death	No	46 (92.0)	289 (95.7)	335 (95.2)	0.21
	Yes	4 (8.0)	13 (4.3)	17 (4.8)	

[a]Fisher's exact test.