Curr Infect Dis Rep (2016) 18: 14
DOI 10.1007/s11908-016-0521-1

Recent Developments in Pediatric Community-Acquired Pneumonia

Russell J. McCulloh[1,2] · **Karisma Patel**[1]

Published online: 10 March 2016

Abstract Community-acquired pneumonia (CAP) is the most common acute infectious cause of death in children worldwide. Consequently, research into the epidemiology, diagnosis, treatment, and prevention of pediatric CAP spans the translational research spectrum. Herein, we aim to review the most significant findings reported by investigators focused on pediatric CAP research that has been reported in 2014 and 2015. Our review focuses on several key areas relevant to the clinical management of CAP. First, we will review recent advances in the understanding of CAP epidemiology worldwide, including the role of vaccination in the prevention of pediatric CAP. We also report on the expanding role of existing and emerging diagnostic technologies in CAP classification and management, as well as advances in optimizing antimicrobial use. Finally, we will review CAP management from the policy and future endeavors standpoint, including the influence of clinical practice guidelines on clinician management and patient outcomes, and future potential research directions that are in the early stages of investigation.

Keywords Community-acquired pneumonia · Pediatric · Pneumococcus · Molecular diagnostics · Viral pneumonia

This article is part of the Topical Collection on *Respiratory Infections*

✉ Russell J. McCulloh
rmcculloh@cmh.edu

[1] Division of Infectious Diseases, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO 64108, USA

[2] Pediatrics and Internal Medicine, University of Missouri–Kansas City, Kansas City, MO, USA

Introduction

Pneumonia is the single greatest cause of death due to infection in children worldwide, accounting for roughly 15 % of deaths among children <5 years old [1]. Nearly one in 500 children under the age of 5 years will be hospitalized for community-acquired pneumonia (CAP) annually [2]. The costs to treat one case of pediatric CAP can exceed US $11,000 [3], and the burden to diagnose and treat pediatric CAP in 66 of the 75 "countdown to 2015: countries for maternal, newborn, and child survival" is approximately US $109 million annually [1]. Thus, pediatric CAP is a widespread problem of profound economic and social importance to children and communities worldwide.

Despite the high prevalence of CAP in children, clinicians and public health experts face ongoing challenges in regards to the accurate diagnosis, optimal management, and prevention of CAP. Consequently, research in pediatric CAP is a broad-based, global endeavor encompassing a wide array of disciplines. Medline indexed more than 200 new articles focused on pediatric CAP from 2014 through the first half of 2015. These articles ranged from early translational research focused on pneumonia pathophysiology, diagnostic test development, and identification of potential therapeutic agents, to clinical trials of existing and newer antimicrobials and management strategies, to population-level studies of CAP epidemiology, resource use, health outcomes, and cost. Herein, we attempt to summarize the most salient and momentous recent findings in pediatric CAP.

Advances/Developments in CAP Epidemiology

New Insights into Microbiological Epidemiology of CAP

The widespread implementation of PCR-based respiratory pathogen testing has prompted a flurry of reports describing the

epidemiology of viral and bacterial infections in CAP. The Etiology of Pneumonia in the Community (EPIC) study, involving three US health systems, found that the annual incidence of CAP was 15.7 cases/10,000 children, with viral pathogens alone responsible for 66 % of cases, bacterial pathogens in 8 % of cases, and mixed bacterial-viral infections in 7 % of cases [4•]. A single-site study in France using bacterial cultures and biplex rt-PCR tests for common respiratory viral pathogens, *Mycoplasma pneumoniae* (MP) and *Chlamydia pneumoniae* (CP) found that, of children evaluated in the emergency department (ED) for CAP, 4.7 % had exclusive bacterial infection, 62.4 % had exclusive viral infections, and 28.2 % were co-infected [5]. In a study of Swedish children ≤5 years diagnosed with viral CAP [6], influenza virus, human metapneumovirus (hMPV), and respiratory syncytial virus (RSV) accounted for 60 % of identified viruses [7], which were similar to findings reported from the EPIC study. Conversely, a recently published meta-analysis of viral CAP incidence as determined by PCR-based methods found that rhinovirus and human bocaviruses were more commonly identified than influenza viruses [8]. A systematic review of reports on CAP etiology across Southeast Asia found that the most common bacterial pathogens identified in pediatric CAP remained pneumococcus and *H. influenzae*, but that *Klebsiella pneumoniae* and *Burkholderia pseudomallei* were also detected in more severe cases, though these organisms were primarily identified in adult patients [9]. Several studies reported the incidence of atypical pathogens, all of which found MP to be most commonly identified [10, 11]. Children diagnosed with CAP due to MP were reported to more often present with wheezing and headache [12], and a Taiwanese study found that children <5 years old with MP CAP may develop more severe illness [13]. However, findings from a Chinese study suggest this risk may be attenuated in children <5 months old [14]. Finally, enterovirus D-68 was responsible for multiple outbreaks of acute LRTI in 2014 [15–18], which previously had been described to cause only sporadic infection.

Reports of antibiotic resistance among common bacterial pathogens vary widely by region. Six years of pneumococcal isolates from a tertiary health center in rural India found 100 % susceptibility to penicillin and macrolides [19], whereas resistance was reported in up to 35 % of isolates from Cambodia, Thailand, and Vietnam [9]. Macrolide resistance was only 3.5 % among the 176 isolates of *M. pneumoniae* from the CDC EPIC study [20], which is similar to rates reported in 2014 among Swiss children (2.0 %) [21].

Effects of Vaccination on CAP Epidemiology

Multiple recent reports document a significant reduction in both CAP and invasive pneumococcal disease (IPD) after widespread uptake of pneumococcal conjugate vaccine (PCV). Vaccination with the 10-valent conjugated pneumococcal vaccine (PCV-10) in a randomized trial of Argentinian, Panamanian, and Colombian infants demonstrated efficacy against bacterial CAP of 18–23 % [22]. A Brazilian study found a 40 % decrease in CAP incidence after introduction of PCV-10 [23], and an observational study of eight pediatric EDs in France before and after PCV-13 introduction found a 16 % decrease in cases of CAP, with the greatest reduction among infants (32 %) [24]. Cases involving pleural effusions and confirmed pneumococcal cases also declined significantly after PCV-13 vaccine implementation. Reductions in pneumococcal pneumonia incidence after PCV-13 release, particularly vaccine-covered strains, were reported in Israel [25], Japan [26], and Uruguay [27]. A Belgian study also found that most cases of pneumococcal pneumonia were caused by non-PCV-7 strains after widespread introduction of the vaccine [28]. Finally, a cost-effectiveness analysis of expanding influenza vaccination to all children and adolescents in Germany estimated that, with only 50 % vaccine uptake, roughly 130,000 cases of CAP would be prevented annually [29••].

Insights into Epidemiological Risk Factors

Several demographic and clinical factors were reported to potentially indicate children at increased risk for severe CAP. The EPIC study team reported that smoking exposure was associated with patients experiencing longer length of stay (LOS) and a greater likelihood to receive intensive care [30]. Smoking, low maternal education, low family income, and poor access to medical care were also identified as risk factors for severe CAP in a prospective longitudinal cohort study of Egyptian children [31]. In a prospective study of CAP in children ≤6 years old conducted at 11 hospitals in Northern England, researchers identified presence of confirmed bacterial infection and prior use of ibuprofen as potential risk factors for developing empyema [32]. Premature birth was associated with increased risk of RSV-associated CAP [33]. Finally, a genetic study evaluating the potential association of allelic differences in the gene encoding interleukin-6 (a pro-inflammatory cytokine that plays a role in the response to pulmonary infections) with risk of developing CAP found that the presence of the GG allele was more likely among Egyptian children diagnosed with CAP, but that this allele was conversely less likely to present among patients who developed sepsis [34].

Access to a primary care provider may also influence CAP management and clinical outcomes. In a case-control study of risk factors for pneumonia hospitalization conducted in New Zealand, children were more likely to present to the ED if they lacked a general practitioner (GP) or if their GP worked ≤20 h/week, but were less likely to be hospitalized [35]. Conversely, outpatient antibiotic therapy prescribed prior to ED presentation was associated with greater odds of hospital admission. A co-diagnosis of acute asthma among children hospitalized for CAP was associated with increased variability in care and overall costs [36].

The Continuing Challenge of Accurate CAP Diagnosis

The clinical diagnosis of CAP remains challenging. Gold-standard microbiological testing often fails to identify a pathogen, and the optimal role and modality for imaging, microbiological, and supplemental biomarker testing remains unclear. Consequently, clinician practice in the evaluation and management of CAP varies widely. For example, a recent evaluation of ED physician versus pediatric hospitalist management of suspected pediatric CAP highlights this issue. In a retrospective analysis of ED versus inpatient physician diagnosis of CAP from the US, researchers found that hospitalists' diagnosis of CAP differed from ED physician diagnosis in 47 % of admissions for acute respiratory illness, and hospitalists stopped ED-initiated antibiotics in 62 % of cases [37]. Research on both existing and emerging diagnostic technologies now aims to reduce uncertainty in CAP diagnosis and etiology.

The Ongoing Debate over Blood Cultures

Several studies have recently examined the practice and clinical implications of blood culture collection. In a prospective study of blood culture obtainment in 171 children hospitalized with CAP at a tertiary medical center in Malaysia, researchers found the pathogen detection rate was 1.2 % and the contamination rate was 1.8 %, with only one patient having antibiotics changed in response to blood culture results [38]. A retrospective review of children hospitalized for acute infections, including CAP in otherwise well children, found that 99 % of blood cultures were either negative or grew a contaminant [39]. A systematic review of studies of blood culture findings in pediatric CAP from 1970 to 2013 found that overall rates of blood cultures positive for a pathogen was 5.1 %, with higher rates of identification among children with severe CAP (9.9 %) and an overall contamination rate of 14.7 % [40]. Furthermore, a four-site retrospective analysis of the associated impact of blood culture obtainment on clinical course and outcomes found that, compared to children who did not have blood cultures obtained, patients hospitalized for CAP who had blood cultures obtained stayed in the hospital 0.8 days longer [41].

New and Emerging Diagnostic and Prognostic Assays

Diagnostic capabilities for identifying causative pathogens in pediatric CAP have rapidly expanded in the past several years for viral pathogens. In particular, the use of multiplex PCR testing for respiratory viruses, MP, and CP has allowed for improved identification of CAP etiology, as noted above. Although multiplex PCR testing for respiratory viral pathogens has enhanced detection rates of pathogens for CAP, its role in affecting clinical management remains uncertain [42, 43]. A recent study also demonstrated the potential of testing parapneumonic effusions using uniplex PCRs for common bacterial pathogens. Investigators identified a causative organism in 82 % of 56 children who had parapneumonic effusions, versus only 25 % using pleural fluid culture [44]. Loop-mediated isothermal amplification (LAMP) may prove useful in rapidly identifying MP, based on a Japanese study reporting that 96 % of cases of MP diagnosed by paired serology were found using LAMP testing, with only a 2.5-h turn-around time [45].

Several candidate biomarkers, assay panels, and clinical factors for diagnosing and predicting severe or complicated pneumonia have also recently been evaluated. Proadrenomedullin was reported to have a sensitivity and specificity for bacteremic pneumonia diagnosis of 100 and 70 %, respectively in a study of 88 children hospitalized with CAP [46]. A study of CAP etiology at two hospitals in the UK found that, among 401 children with CAP, a combination of age, CRP, and neutrophil count differentiated viral from bacterial CAP with a 75.7 % sensitivity and 89.4 % specificity [47], and CRP elevation may predict LOS and fever duration [48]. Procalcitonin was reported to be more highly elevated among children with CAP and pleural effusion than those without [49], and may help distinguish viral from bacterial CAP [50]. Other biomarkers under investigation include soluble plasminogen activator receptor [51] and copeptin [52].

The Role of Chest Ultrasound

Ultrasound (US) evaluation for pneumonia has the benefit of sparing a child exposure to X-ray radiation, which may explain why several studies have recently reported on the performance characteristics of chest US in diagnosing CAP. Compared to chest radiography, studies have reported negative predictive values of 93–94.0 % and positive predictive values of 98.1–100 % with enhanced detection of pleural effusion [53–56]. Chest US findings of impaired perfusion correlated well with CT findings of necrotizing pneumonia [57].

Antimicrobial Therapy

The 2011 Pediatric Infectious Diseases Society and Infectious Diseases Society of America (PIDS/IDSA) guidelines outlined recommendations for the management of CAP in children, including the avoidance of antibiotics in preschool-aged children without clear evidence of bacterial infection, using narrow-spectrum antibiotics (ampicillin and penicillin) in most mild to moderate cases, and reserving macrolide therapy for school-age children with suspected atypical pneumonia [58]. As noted above, clinicians face persistent difficulty

accurately identifying the specific etiology of CAP, resulting in significant variability in prescribing practices.

The rationale for using narrow-spectrum therapy is to help reduce bacterial resistance and decrease the use of unnecessary broad-spectrum antibiotics. When comparing the clinical outcomes of narrow-spectrum to broad-spectrum antibiotic use in hospitalized children with pneumonia, no significant differences were found in LOS, duration of intravenous therapy, readmission rates, or overall costs [59, 60••, 61]. Conversely, Breuer et al. found that treatment with broad-spectrum antibiotics resulted in a shorter hospital stay, shorter duration of fever, and shorter duration of IV treatment in children who received oral therapy for CAP prior to hospitalization [62].

The clinical benefit of azithromycin use for the treatment of MP remains inconclusive, based on two recently published systematic reviews [63, 64]. Ambroggio et al. compared the efficacy of beta-lactam and macrolide monotherapy in children, and found no differences in the likelihood of treatment failure regardless of age [65]. Conversely, the addition of macrolide use was shown to result in a shorter LOS in school-aged children, but not in younger children [66]. Overall, azithromycin use for CAP treatment remains controversial due to unclear efficacy, high rates of *S. pneumoniae* resistance [67], and the potential for unnecessary adverse effects.

In cases of complicated pneumonia and/or concern for resistant-*S. pneumoniae*, levofloxacin remains a potential treatment option. Practitioners continue to be hesitant in prescribing fluoroquinolones in children due to the risk of developing fluoroquinolone resistance [68], as well as the risk for adverse events, such as *Clostridium difficile* colitis [69]. Additionally, although the US Food and Drug Administration has placed a black-box warning regarding the risk of tendon disorders and fluoroquinolone use, clinical evidence to support this link in children is conflicting [70]. A 5-year follow-up study evaluating the presence of musculoskeletal adverse events (MSAEs) in children receiving levofloxacin for CAP treatment found no clinically detectable difference in MSAEs between levofloxacin and comparator groups. Furthermore, no cases of MSAE were thought to be related to use of the study drug, suggesting that the risk of cartilage injury with levofloxacin use is low [71].

The role of adjunctive therapy with corticosteroids is a new area of interest. In the setting of refractory MP pneumonia, three-day methylprednisolone pulse therapy has been suggested to help suppress hyperactive cellular immunity and the associated inflammatory response [72, 73]. A case report has also suggested potential use in pneumococcal pneumonia; however, further prospective trials are needed [74].

Due to the lack of comparative studies, there is insufficient evidence to support an optimal duration of antibiotic therapy for CAP. A recent randomized trial by Greenberg et al. found that a 5-day oral treatment with amoxicillin was as effective as a 10-day course in children 6–59 months old with non-severe CAP [75]. Additionally, a systematic review on antibiotic therapy for CAP in children 2–59 months suggests that non-severe CAP can be treated with a course as short as 3 days [76]. The potential benefits of a shorter antibiotic course include lower costs, reduction of antimicrobial resistance, improvement in patient compliance, and reduction of associated adverse effects. The appropriate duration remains unknown for severe pneumonia [77].

Clinical Practice Guidelines and Their Role in Changing Practice

Evidence of Variation in Care for Pediatric CAP

Multiple recent studies have documented significant variation of care in CAP management. A study of US hospital admissions from 2007 to 2010 found that among 17,299 pneumonia patients diagnosed at a broad array of hospitals of varying size and geographic location, three-fourths of children had blood cultures obtained, 88 % underwent chest radiography and had complete blood counts, and up to 20 % had a CRP obtained, with significant variation in utilization identified across hospitals [78]. Only 0.2 % of patients received narrow-spectrum antibiotics. A retrospective study of outpatient antibiotic prescribing in a large Midwest health system found that 47 % of children <5 years of age treated for CAP were prescribed a macrolide [79], and a study of antibiotic prescribing for severe pneumonia in Sudanese children found only 18 % concordance with WHO guidelines, which represents significant opportunities for improvement [80].

Impact of Guidelines on Clinical Care and Outcomes

Several recent studies have been published that support the utility and potential benefits of local and national clinical practice guidelines. First, a prospective observational study of 11 hospitals in Northern England between time periods before and after release of a national CPG in 2002 found that, for children treated empirically for CAP, rates of diagnostic test performance generally fell and oral antibiotic use increased, in accordance with guideline recommendations [81]. In a single-site, retrospective study of inpatient CAP management, guideline-concordant antibiotic therapy did not compromise clinical outcomes, hospital LOS, or affect patient costs [82]. Adherence to guidelines was also not associated with changes in treatment failure rates in one Kenyan study [83]. A retrospective study of antibiotic prescribing practices for inpatients with CAP at 43 children's hospitals found that use of narrow-spectrum antibiotics for treating CAP increased from 28 to 43 % after the 2011 PIDS/IDSA guidelines were released [84], and similar increases were reported in the EPIC study [85]. Finally, use of quality improvement methods was reported to increase the proportion of children hospitalized with

CAP who had blood cultures obtained at a tertiary children's hospital from 53 to 90 % over a 6-month period, demonstrating the potential utility of these methods to help translate clinical practice guidelines into changes in patient care [86].

Future Directions

Emerging avenues for research in CAP continue to span the spectrum from bench to bedside applications. Advances in gene expression profiling have been proposed as a future means to improve the diagnosis and management of children with CAP by determining the etiology and severity of infection, though issues of cost, utility, and logistics must first be addressed [87]. A small study has reported that shared decision-making as a bedside intervention may aid in optimizing antibiotic use and improve parent/patient satisfaction when treating children with CAP [88], although future larger-scale studies are needed to fully evaluate this intervention. Finally, although recent reports of efforts to reduce antibiotic use in non-bacterial CAP through the implementation of combined clinical/laboratory result-based decision rules demonstrate promising results [89], larger-scale studies and new approaches that leverage newer diagnostic technologies and antimicrobial stewardship efforts have yet to be performed.

Conclusions

Our review of recent advances in pediatric CAP has revealed that this common and costly cause of infectious morbidity and mortality in children remains the focus of multidisciplinary research and health policy intervention. The years 2014–2015 have yielded new insights into the effectiveness of current prevention and treatment strategies. Results from recent large-scale studies have enhanced our understanding of the myriad of bacterial and (especially) viral etiologies responsible for pediatric CAP and the role of newer molecular diagnostic techniques in determining CAP etiology. Efforts to harmonize clinical practice with existing and emerging evidence and improving diagnostic technologies appear to be having an effect on clinical practice, although further efforts are clearly needed to optimize care delivery and clinical outcomes.

Compliance with Ethics Standards

Conflict of Interest Dr. McCulloh reports that their research is funded by a Novice Research Award from the Gerber Foundation and a clinical scholar award from Eva and Kenneth Smith Foundation.

Dr. Patel has no conflicts of interests to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. World Health Organization. Pneumonia. Fact sheet No. 331. 2014.
2. Lee GE et al. National hospitalization trends for pediatric pneumonia and associated complications. Pediatrics. 2010;126(2):204–13.
3. Keitel K et al. Observed costs and health care use of children in a prospective cohort study on community-acquired pneumonia in Geneva. Switzerland Swiss Med Wkly. 2014;144:w13925.
4. • Jain S et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015;372(9):835–45. **This article reports on the results of the largest epidemiological study of pediatric CAP in children to date. Additionally, the use of multiple pathogen detection methods provides unprecedented insight into causative etiologies for CAP, particularly viral causes**.
5. Cantais A et al. Epidemiology and microbiological investigations of community-acquired pneumonia in children admitted at the emergency department of a university hospital. J Clin Virol. 2014;60(4): 402–7.
6. Self WH, et al. Respiratory viral detection in children and adults: comparing asymptomatic controls and patients with community-acquired pneumonia. J Infect Dis. 2015.
7. Rhedin S et al. Respiratory viruses associated with community-acquired pneumonia in children: matched case-control study. Thorax. 2015;70(9):847–53.
8. Wang M et al. Incidence of viral infection detected by PCR and real-time PCR in childhood community-acquired pneumonia: a meta-analysis. Respirology. 2015;20(3):405–12.
9. Goyet S et al. Etiologies and resistance profiles of bacterial community-acquired pneumonia in Cambodian and neighboring countries' health care settings: a systematic review (1995 to 2012). PLoS One. 2014;9(3), e89637.
10. Chen K et al. The aetiology of community associated pneumonia in children in Nanjing, China and aetiological patterns associated with age and season. BMC Public Health. 2015;15:113.
11. Huong Ple T 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.
12. Medjo B et al. Mycoplasma pneumoniae as a causative agent of community-acquired pneumonia in children: clinical features and laboratory diagnosis. Ital J Pediatr. 2014;40:104.
13. Ma YJ, et al. Clinical and epidemiological characteristics in children with community-acquired mycoplasma pneumonia in Taiwan: a nationwide surveillance. J Microbiol Immunol Infect. 2014; 632–8.
14. Sun H et al. Epidemiology and clinical profiles of Mycoplasma pneumoniae infection in hospitalized infants younger than one year. Respir Med. 2015;109(6):751–7.
15. Esposito S et al. Enterovirus D68-associated community-acquired pneumonia in children living in Milan. Italy J Clin Virol. 2015;68: 94–6.
16. Imamura T, Oshitani H. Global reemergence of enterovirus D68 as an important pathogen for acute respiratory infections. Rev Med Virol. 2015;25(2):102–14.
17. Bragstad K et al. High frequency of enterovirus D68 in children hospitalised with respiratory illness in Norway, autumn 2014. Influenza Other Respir Viruses. 2015;9(2):59–63.
18. Schuster JE et al. Severe enterovirus 68 respiratory illness in children requiring intensive care management. J Clin Virol. 2015;70: 77–82.

19. Deva A et al. Pneumococcal infections at a rural tertiary care hospital: a seven year study on isolation rate, clinical spectrum and antibiogram. J Clin Diagn Res. 2014;8(2):50–2.
20. Diaz MH et al. Molecular detection and characterization of Mycoplasma pneumoniae among patients hospitalized with community-acquired pneumonia in the United States. Open Forum Infect Dis. 2015;2(3):ofv106.
21. Meyer Sauteur PM et al. Survey of macrolide-resistant Mycoplasma pneumoniae in children with community-acquired pneumonia in Switzerland. Swiss Med Wkly. 2014;144:w14041.
22. Tregnaghi MW et al. Efficacy of pneumococcal nontypable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in young Latin American children: a double-blind randomized controlled trial. PLoS Med. 2014;11(6), e1001657.
23. Abrao WM et al. Impact of the antipneumococcal conjugate vaccine on the occurrence of infectious respiratory diseases and hospitalization rates in children. Rev Soc Bras Med Trop. 2015;48(1): 44–9.
24. Angoulvant F et al. Early impact of 13-valent pneumococcal conjugate vaccine on community-acquired pneumonia in children. Clin Infect Dis. 2014;58(7):918–24.
25. Greenberg D et al. Impact of PCV7/PCV13 introduction on community-acquired alveolar pneumonia in children <5 years. Vaccine. 2015;33(36):4623–9.
26. Naito S, et al. The impact of heptavalent pneumococcal conjugate vaccine on the incidence of childhood community-acquired pneumonia and bacteriologically confirmed pneumococcal pneumonia in Japan. Epidemiol Infect. 2015; 1–13.
27. Pirez MC et al. Changes in hospitalizations for pneumonia after universal vaccination with pneumococcal conjugate vaccines 7/13 valent and Haemophilus influenzae type b conjugate vaccine in a pediatric referral hospital in Uruguay. Pediatr Infect Dis J. 2014;33(7):753–9.
28. De Schutter I et al. Pneumococcal aetiology and serotype distribution in paediatric community-acquired pneumonia. PLoS One. 2014;9(2), e89013.
29.•• Damm O et al. Public health impact and cost-effectiveness of intranasal live attenuated influenza vaccination of children in Germany. Eur J Health Econ. 2015;16(5):471–88. **This article provides country-level data regarding the potential benefit of widespread influenza vaccination, including expected numbers of averted cases of viral pneumonia. Such information is important for clinicians, public health officials, and third-party payers to consider in decisions of vaccine administration and policy**.
30. Ahn A, et al. Secondhand smoke exposure and illness severity among children hospitalized with pneumonia. J Pediatr. 2015; 869–74.
31. Azab SF et al. Impact of the socioeconomic status on the severity and outcome of community-acquired pneumonia among Egyptian children: a cohort study. Infect Dis Poverty. 2014;3:14.
32. Elemraid MA et al. Risk factors for the development of pleural empyema in children. Pediatr Pulmonol. 2015;50(7):721–6.
33. Greenberg D et al. Increased risk for respiratory syncytial virus-associated, community-acquired alveolar pneumonia in infants born at 31–36 weeks of gestation. Pediatr Infect Dis J. 2014;33(4):381–6.
34. Zidan HE, Elbehedy RM, Azab SF. IL6-174 G/C gene polymorphism and its relation to serum IL6 in Egyptian children with community-acquired pneumonia. Cytokine. 2014;67(2):60–4.
35. Emery DP et al. The impact of primary care on emergency department presentation and hospital admission with pneumonia: a case-control study of preschool-aged children. NPJ Prim Care Respir Med. 2015;25:14113.
36. Wilson KM et al. Hospitalization for community-acquired pneumonia in children: effect of an asthma codiagnosis. Hosp Pediatr. 2015;5(8):415–22.
37. Coon ER, Maloney CG, Shen MW. Antibiotic and diagnostic discordance between ED physicians and hospitalists for pediatric respiratory illness. Hosp Pediatr. 2015;5(3):111–8.
38. Lai EM et al. Should all children admitted with community acquired pneumonia have blood cultures taken? Indian J Pediatr. 2015;82(5):439–44.
39. Parikh K, Davis AB, Pavuluri P. Do we need this blood culture? Hosp Pediatr. 2014;4(2):78–84.
40. Iroh Tam PY et al. Blood culture in evaluation of pediatric community-acquired pneumonia: a systematic review and meta-analysis. Hosp Pediatr. 2015;5(6):324–36.
41. McCulloh RJ et al. Evaluating the use of blood cultures in the management of children hospitalized for community-acquired pneumonia. PLoS One. 2015;10(2), e0117462.
42. Schulert GS, Hain PD, Williams DJ. Utilization of viral molecular diagnostics among children hospitalized with community acquired pneumonia. Hosp Pediatr. 2014;4(6):372–6.
43. McCulloh RJ et al. Potential utility of multiplex amplification respiratory viral panel testing in the management of acute respiratory infection in children: a retrospective analysis. Journal of the Pediatric Infectious Diseases Society. 2014;3(2):146–53.
44. Pernica JM et al. Real-time polymerase chain reaction for microbiological diagnosis of parapneumonic effusions in Canadian children. Can J Infect Dis Med Microbiol. 2014;25(3):151–4.
45. Aizawa Y et al. Clinical utility of loop-mediated isothermal amplification for rapid diagnosis of Mycoplasma pneumoniae in children. J Med Microbiol. 2014;63(Pt 2):248–51.
46. Alcoba G et al. Proadrenomedullin and copeptin in pediatric pneumonia: a prospective diagnostic accuracy study. BMC Infect Dis. 2015;15(1):347.
47. Elemraid MA et al. Utility of inflammatory markers in predicting the aetiology of pneumonia in children. Diagn Microbiol Infect Dis. 2014;79(4):458–62.
48. Williams DJ et al. Association of white blood cell count and C-reactive protein with outcomes in children hospitalized for community-acquired pneumonia. Pediatr Infect Dis J. 2015;34(7): 792–3.
49. Fonseca TS, et al. Pleural effusion increases serum procalcitonin values in children with community-acquired pneumonia. Pediatr Infect Dis J. 2015; 914–5.
50. Hoshina T et al. The utility of biomarkers in differentiating bacterial from non-bacterial lower respiratory tract infection in hospitalized children: difference of the diagnostic performance between acute pneumonia and bronchitis. J Infect Chemother. 2014;20(10):616–20.
51. Wrotek A, Jackowska T, Pawlik K. Soluble urokinase plasminogen activator receptor: an indicator of pneumonia severity in children. Adv Exp Med Biol. 2015;835:1–7.
52. Wrotek A, Jackowska T, Pawlik K. Sodium and copeptin levels in children with community acquired pneumonia. Adv Exp Med Biol. 2015;835:31–6.
53. Esposito S et al. Performance of lung ultrasonography in children with community-acquired pneumonia. Ital J Pediatr. 2014;40:37.
54. Urbankowska E., et al. Lung ultrasound in the diagnosis and monitoring of community acquired pneumonia in children. Respir Med. 2015; 1207–12.
55. Reali F et al. Can lung ultrasound replace chest radiography for the diagnosis of pneumonia in hospitalized children? Respiration. 2014;88(2):112–5.
56. Ho MC et al. Usefulness of lung ultrasound in the diagnosis of community-acquired pneumonia in children. Pediatr Neonatol. 2015;56(1):40–5.
57. Lai SH, Wong KS, Liao SL. Value of lung ultrasonography in the diagnosis and outcome prediction of pediatric community-acquired pneumonia with necrotizing change. PLoS One. 2015;10(6), e0130082.

58. Bradley JS et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011;53(7):e25–76.
59. Selby A, Pettit K, Brown N. Narrow-spectrum antibiotics are as effective as broad-spectrum antibiotics in the treatment of community-acquired pneumonia. Arch Dis Child Educ Pract Ed. 2015;100(4):223.
60.•• Queen MA et al. Comparative effectiveness of empiric antibiotics for community-acquired pneumonia. Pediatrics. 2014;133(1):e23–9. **This multicenter, retrospective study found that narrow-spectrum antibiotic use for children hospitalized with CAP resulted in similar outcomes to broad-spectrum antibiotic use. This study provides supporting evidence for the national guideline's recommendation to use narrow-spectrum antibiotics as first-line therapy for children hospitalized with CAP.**
61. Amarilyo G et al. IV Penicillin G is as effective as IV cefuroxime in treating community-acquired pneumonia in children. Am J Ther. 2014;21(2):81–4.
62. Breuer O et al. Antibiotic treatment for children hospitalized with community-acquired pneumonia after oral therapy. Pediatr Pulmonol. 2015;50(5):495–502.
63. Biondi E et al. Treatment of mycoplasma pneumonia: a systematic review. Pediatrics. 2014;133(6):1081–90.
64. Gardiner SJ, Gavranich JB, Chang AB. Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children. Cochrane Database Syst Rev. 2015;1, CD004875.
65. Ambroggio L, et al. Comparative effectiveness of beta-lactam vs. macrolide monotherapy in children with pneumonia diagnosed in the outpatient setting. Pediatr Infect Dis J. 2015; 839–42.
66. Leyenaar JK et al. Comparative effectiveness of ceftriaxone in combination with a macrolide compared with ceftriaxone alone for pediatric patients hospitalized with community-acquired pneumonia. Pediatr Infect Dis J. 2014;33(4):387–92.
67. Zhanel GG et al. Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant Streptococcus pneumoniae: analysis of phase 3 clinical trial data. J Antimicrob Chemother. 2014;69(10):2835–40.
68. Adam HJ et al. Association between fluoroquinolone usage and a dramatic rise in ciprofloxacin-resistant Streptococcus pneumoniae in Canada, 1997–2006. Int J Antimicrob Agents. 2009;34(1):82–5.
69. Deshpande A et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. J Antimicrob Chemother. 2013;68(9):1951–61.
70. Bradley JS et al. The use of systemic and topical fluoroquinolones. Pediatrics. 2011;128(4):e1034–45.
71. Bradley JS et al. Assessment of musculoskeletal toxicity 5 years after therapy with levofloxacin. Pediatrics. 2014;134(1):e146–53.
72. You SY et al. Effects of methylprednisolone pulse therapy on refractory Mycoplasma pneumoniae pneumonia in children. Allergy Asthma Immunol Res. 2014;6(1):22–6.
73. Izumikawa K et al. Clinical features, risk factors and treatment of fulminant Mycoplasma pneumoniae pneumonia: a review of the Japanese literature. J Infect Chemother. 2014;20(3):181–5.
74. Lavi E et al. Systemic steroid treatment for severe expanding pneumococcal pneumonia. Case Rep Pediatr. 2015;2015:186302.
75. Greenberg D et al. Short-course antibiotic treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind, randomized, placebo-controlled trial. Pediatr Infect Dis J. 2014;33(2):136–42.
76. Lassi ZS et al. Systematic review on antibiotic therapy for pneumonia in children between 2 and 59 months of age. Arch Dis Child. 2014;99(7):687–93.
77. Lassi ZS, Imdad A, Bhutta ZA. Short-course versus long-course intravenous therapy with the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months. Cochrane Database Syst Rev. 2015;6, CD008032.
78. Leyenaar JK et al. Variation in resource utilization for the management of uncomplicated community-acquired pneumonia across community and children's hospitals. J Pediatr. 2014;165(3):585–91.
79. Saleh EA, et al. Guideline-concordant antibiotic prescribing for pediatric outpatients with otitis media, community-acquired pneumonia, and skin and soft tissue infections in a large multispecialty healthcare system. Clin Res Infect Dis. 2015. 2(1).
80. Salih KE et al. Poor adherence to the world health organization guidelines of treatment of severe pneumonia in children at Khartoum. Sudan BMC Res Notes. 2014;7:531.
81. Elemraid MA et al. Changing clinical practice: management of paediatric community-acquired pneumonia. J Eval Clin Pract. 2014;20(1):94–9.
82. Thomson J et al. Hospital outcomes associated with guideline-recommended antibiotic therapy for pediatric pneumonia. J Hosp Med. 2015;10(1):13–8.
83. Agweyu A et al. Prevalence and correlates of treatment failure among Kenyan children hospitalised with severe community-acquired pneumonia: a prospective study of the clinical effectiveness of WHO pneumonia case management guidelines. Trop Med Int Health. 2014;19(11):1310–20.
84. Ross RK et al. Impact of Infectious Diseases Society of America/Pediatric Infectious Diseases Society Guidelines on treatment of community-acquired pneumonia in hospitalized children. Clin Infect Dis. 2014;58(6):834–8.
85. Williams DJ et al. Antibiotic choice for children hospitalized with pneumonia and adherence to national guidelines. Pediatrics. 2015;136(1):44–52.
86. Murtagh Kurowski E et al. Improvement methodology increases guideline recommended blood cultures in children with pneumonia. Pediatrics. 2015;135(4):e1052–9.
87. Wallihan R, Ramilo O. Community-acquired pneumonia in children: current challenges and future directions. J Infect. 2014;69 Suppl 1:S87–90.
88. Rosati P, et al. Are parents of children hospitalized with severe community-acquired pneumonia more satisfied with care when physicians allow them to share decisions on the antibiotic route? Health Expect. 2014.
89. Ferrero F et al. Effectiveness and safety of a clinical decision rule for guiding the management of children with pneumonia vaccinated against pneumococcal disease: a controlled clinical trial. Arch Argent Pediatr. 2015;113(5):397–403.