

What Are the Common Causes of Childhood Pneumonia In Developing Countries?

Primary Reviewers: Philip Ayieko¹; Mike English^{1, 2}

Secondary Reviewer: Kim Mulholland³

¹ Kenya Medical Research Institute/ Wellcome Trust Collaboration, Nairobi, Kenya

² Department of Paediatrics, University of Oxford, Oxford, UK.

³ Department of Paediatrics, University of Melbourne, Australia.

The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: ***What Are the Common Causes of Childhood Pneumonia In Developing Countries?***

The **WHO Pocketbook of Hospital Care for Children** states that Pneumonia is usually caused by viruses or bacteria. Most serious episodes are caused by bacteria. It is usually not possible, however, to determine the specific cause by clinical features or chest X-ray appearance. Pneumonia is classified as very severe, severe or non-severe, based on the clinical features, with specific treatment for each of them. Antibiotic therapy is needed in all cases. (Pocketbook chapter 4.2, page 72).

Introduction:

Pneumonia in infants and children remains a significant problem worldwide. Current WHO treatment recommendations for low and middle income countries (LMICs) are largely based on the most likely aetiological organisms identified in studies conducted before or around the period when the guidelines were developed over 15 years ago.^{1,2} We were interested in whether more recent studies, possibly conducted with newer diagnostic techniques, continue to support previous data on aetiology in LMICs and therefore provide continued support for the empiric case management guidelines. In

reviewing the literature it is clear that there are still problems with assigning an aetiological cause to childhood episodes of pneumonia. In a symptomatic child a pathogen identified in blood culture is widely regarded as the causal agent of pneumonia. However, this means of identifying organisms is only useful when pneumonia is associated with bacteraemia and the technique is considerably less sensitive than other tests such as lung aspiration (lung puncture).^{3,4} While, lung aspiration provides substantially more information regarding the bacterial aetiology of pneumonia it is a technique suitable only for more severely ill children with specific radiological findings presenting to research centres. More recent diagnostic techniques (including serology, immunofluorescence, viral culture, sputum induction and others) may be used on children with a range of presentations. As such techniques are added to the portfolio of tools used it appears likely that the observed pattern of aetiological agents will change providing us with a more complete understanding of the true burden of pneumonia attributable to different aetiological agents.⁵

In addition, recent studies have utilised two alternative, indirect methods of looking at aetiology. The first, the "vaccine probe" approach uses a vaccine to define the burden of vaccine-preventable disease within a population.^{6,7} The second evaluates the impact of introducing antibiotics on pneumonia specific case fatality rates, providing a measure of the contribution of bacteria to mortality.⁸ As vaccines such as that against *Haemophilus influenzae* Type B (Hib) and the pneumococcal conjugate vaccines are introduced routinely they will further change the aetiology of pneumonia, with 'atypical pathogens' likely to become proportionately more

important. In addition, the maturing HIV epidemic has already probably resulted in a change in the spectrum of pathogens causing pneumonia particularly in African children.^{9, 10} The extent to which these changes impact on treatment recommendations is not yet clear.

Methodology

Search strategy and quality review

Potential studies for inclusion were identified by direct searches of MEDLINE database through PubMed targeting the years 1990 to date. The following combinations of search terms were used:

Blood culture: Pneumonia AND (etiology OR epidemiology OR cause OR microbiolog* OR pathogen) AND “blood culture” AND child*

Lung puncture: Pneumonia AND (etiology OR epidemiology OR pathogen) AND (“lung puncture” OR “lung aspirat*” OR “lung tap”)

The specific searches on the different methods used to determine pneumonia aetiology were aimed at identifying available evidence based on recent studies with good reference standards for pneumonia eg radiology (Level 1b). We also included studies using diagnostic findings whose specificity is so high that a positive result rules-in the diagnosis of pneumonia (Level 1c). However, where there were no such studies we briefly report findings based on previous carefully conducted reviews of diagnostic studies. To ensure a comprehensive review, supplementary searches were conducted in the World Health Organisation library database, and reference lists of selected studies. Each author independently reviewed the titles and available abstracts from the retrieved articles, selecting for further review those that identified potential causes of pneumonia in children. We excluded studies conducted in developed countries.

The methodological quality of the selected articles was assessed using the Oxford Center for Evidence Based Medicine (CEBM) levels of evidence scale, which ranks studies in a hierarchy, based on methodological validity, with systematic reviews graded as level 1. Expert opinion on the other hand provides weak (level 5) evidence.

Results

Studies of specific pathogens are summarized in table 1. These are systematic reviews (Level 1a or 2a) or etiology studies with good reference standards (Level 2a, 2b) in which pneumonia was community acquired. Three comprehensive systematic reviews^{3,11,12} of lung puncture studies were selected two being relatively recent. Most of the studies included in these systematic reviews were conducted in Africa, Asia, and Latin America. No post review lung puncture study among children with community acquired pneumonia was identified. Six blood culture studies conducted among bacteraemic children with pneumonia were included in the review.^{4,13} Three studies⁶⁻⁸ that indirectly determined the burden of childhood pneumonia attributable to various pathogens were also selected for inclusion.

Lung puncture and blood culture studies

Since 1990, eleven studies involving 546 lung aspirates have been reported from Africa, Asia, and Papua New Guinea.^{3,11} In South America there was no data from lung puncture studies during the same period. In these studies¹⁴⁻²⁵ the aetiological agent was identified in 278 (51%) out of the 546 cases of pneumonia investigated using lung aspiration. *S. pneumoniae* was found by means of lung taps in 93(33%) of the 278 cases for which the aetiology was identified; *H. influenzae* and *S. aureus* were detected in 18 % and 26% of the cases respectively. However, the majority of staphylococcal isolates came from a single, Nigerian study examining bacterial pathogens in malnourished children with pneumonia.¹⁶ In the other studies reviewed staphylococci were uncommon and often found in children with additional lung pathology (for example measles bronchopneumonia) or in malnourished children. It therefore seems likely that *S. aureus*, while an important pathogen in high risk groups is less commonly a cause of community acquired pneumonia.

Three of the reported studies used both lung puncture and blood culture techniques to identify pneumonia aetiology.^{14,18,24} In one study conducted in The Gambia, 100 children aged between 3 and 58 months with pneumonia were investigated using blood culture and culture of lung or pleural aspirates.¹⁸ In 44 children one species of bacterium was isolated from blood (6), lung culture (30), or both (8), while in eight

children two species were isolated. In four of these eight children, one organism was isolated from blood culture, while a different organism was isolated from lung or pleural aspirate. Twenty five children had both bacterial and viral pathogens, indicating that dual infection is possible. Respiratory syncytial virus (RSV), the most common isolate in well nourished children, accounted for 13% of viral isolates in this group. The viral pathogen most frequently recovered in the other studies that attempted to isolate viruses was also RSV (12% in The Gambia and 14% in India).^{14,24}

In recent blood culture investigations of bacteraemia in children with the clinical signs of pneumonia nontyphoidal *salmonella* has been isolated with increasing frequency in young children. In a Malawian study nontyphoidal *salmonella* were the second most common blood culture isolate after *S pneumoniae* among children with radiologically confirmed severe pneumonia and were more common than *H influenzae*.¹³ In Kenyan children enterobacteriaceae (most frequently nontyphoidal *salmonella*) were also prominent pathogens among admissions with the clinical appearance of pneumonia who had a positive blood culture.⁴

Data from studies conducted in areas where the population prevalence of HIV in adults is high report frequent isolation of *Pneumocystis jiroveci* (the aetiological agent for pneumocystis carinii pneumonia, PCP), with median age of presentation at 2-3 months.²⁶ Thus these data suggest that in all children (both HIV positive and negative) presenting with acute severe pneumonia in the inpatient settings studied the prevalence of *Pneumocystis jiroveci* (carinii) pneumonia (PCP) ranges from 11% to 16.5%.^{26,27} However, in South Africa *P jiroveci* was isolated in 9.9% of HIV positive children presenting with pneumonia.²⁸ The implication being that the prevalence of HIV in children with acute severe pneumonia is likely to be high (contributing to the high overall identification of *Pneumocystis jiroveci*) but that most HIV positive children presenting with pneumonia do not have PCP.

Indirect estimates of causes of pneumonia

The proportion of disease prevented by vaccination will only truly represent the disease burden attributable to the vaccine specific pathogen when the vaccine has an efficacy of 100% and when there is complete case

ascertainment.⁵ As these conditions are not met the fraction of disease prevented by a pathogen specific vaccine will generally underestimate the true, specific disease burden. In The Gambia, the reduction in the overall incidence of radiologically defined pneumonia in children receiving the Hib vaccine, suggested that about 20% of episodes of radiographically defined pneumonia in young Gambian children are due to Hib.²⁹ In Indonesia, a controlled trial designed to estimate incidences of vaccine-preventable Hib pneumonia and meningitis among children younger than 2 years however only resulted in reductions in pneumonia outcomes ranging from 0 - 4.8% (although the vaccine prevented 55% of probable bacterial meningitis and 86% of microbiologically confirmed Hib meningitis).⁷ In a recent, large, Gambian trial of the 9 valent pneumococcal conjugate vaccine, vaccination reduced radiologically confirmed pneumonia by 37%, all cause hospital admission by 15% and all cause mortality by 16%.⁶ While in South Africa the 9 valent pneumococcal vaccine efficacy against radiological pneumonia was 20% in HIV negative and 13% in HIV positive children.³⁰

Summary

S.pneumonia and *H.influenzae* remain the leading causes of childhood bacterial pneumonia in LMICs with greater evidence for a major role for *H.influenzae* in Africa. However, the incidence of *H.influenzae* Type B pneumonia has significantly reduced in areas where routine Hib immunization has been implemented.³¹ While data therefore continue to support the prominent role of long-recognized bacteria as causes of pneumonia, at least amongst hospitalised children with pneumonia in Africa two additional pathogens have recently gained prominence. Non-typhoidal *salmonella*, whether or not reflecting a primary respiratory tract infection, are associated with a clinical presentation consistent with pneumonia, at least in hospitalised cases. The second emergent pathogen in children with severe or complicated pneumonia in Africa is *Pneumocystis jiroveci*. Data on the latter are limited to reports from large, often tertiary hospitals in areas where population prevalence of HIV in adults is high. Furthermore there is some debate over the sensitivity and specificity of the various diagnostic tests that have been used²⁸. What is clear, however, is that detailed aetiological studies of pneumonia, combined with adequate antibiotic susceptibility testing of pathogens, will continue to be required in low income settings if

case management guidelines are to remain relevant.

References

1. WHO. Technical bases for the WHO recommendations on the management of pneumonia in children at first-level health facilities. Geneva: WHO/ARI/91.20, 1991.
2. WHO. Management of the child with a serious infection or severe malnutrition. *Guidelines for care at first-referral level in developing countries*. Geneva. Switzerland, 2000.
3. Scott J, Hall A. The value and complications of percutaneous transthoracic lung aspiration for the etiologic diagnosis of community-acquired pneumonia. *Chest*. 1999;**116**:1716-32.
4. Berkley J, Maitland K, Mwangi I, et al. Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: observational study. *BMJ* 2005;**330**:995.
5. Obaro S, Madhi S. Bacterial pneumonia vaccines and childhood pneumonia: are we winning, refining, or redefining? *Lancet Infect Dis*. 2006;**6**:150-61.
6. Cutts F, Zaman S, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet*. 2005;**365**:1139-46.
7. Gessner B, Sutanto A, Linehan M, et al. Incidences of vaccine-preventable Haemophilus influenzae type b pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial. *Lancet* 2005;**365**:43-52.
8. Sazawal S, Black R, Group. PCMT. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *Lancet Infect Dis*. 2003;**3**:547-56.
9. Graham S, Mtitimila E, Kamanga H, Walsh A, Hart C, Molyneux M. Clinical presentation and outcome of Pneumocystis carinii pneumonia in Malawian children. *Lancet* 2000;**355**(9201):369-73.
10. Bakeera-Kitaka S, Musoke P, Downing R, Tumwine J. Pneumocystis carinii in children with severe pneumonia at Mulago Hospital, Uganda. *Ann Trop Paediatr* 2004;**24**(3):227-35.
11. Vuori-Holopainen E, Peltola H. Reappraisal of lung tap: review of an old method for better etiologic diagnosis of childhood pneumonia. *Clin Infect Dis*. 2001;**32**:715-26.
12. Shann F. Etiology of severe pneumonia in children in developing countries. *Pediatr Infect Dis*. 1986;**5**:247-52.
13. Graham S, Walsh A, Molyneux E, Phiri A, Molyneux M. Clinical presentation of non-typhoidal Salmonella bacteraemia in Malawian children. *Trans R Soc Trop Med Hyg*. 2000;**94**:310-4.
14. Forgie I, O'Neill K, Lloyd-Evans N, et al. Etiology of acute lower respiratory tract infections in Gambian children: II. Acute lower respiratory tract infection in children ages one to nine years presenting at the hospital. *Pediatr Infect Dis J* 1991;**10**(1):42-7.
15. Forgie I, O'Neill K, Lloyd-Evans N, et al. Etiology of acute lower respiratory tract infections in Gambian children: I. Acute lower respiratory tract infections in infants presenting at the hospital. *Pediatr Infect Dis J*. 1991;**10**:33-41.
16. Fagbule D. Bacterial pathogens in malnourished children with pneumonia. *Trop Geogr Med*. 1993;**45**:294-6.
17. O'Dempsey T, McArdle T, Lloyd-Evans N, et al. Importance of enteric bacteria as a cause of pneumonia, meningitis and septicemia among children in a rural community in The Gambia, West Africa. *Pediatr Infect Dis J*. 1994;**13**:122-8.
18. Adegbola R, Falade A, Sam B, et al. The etiology of pneumonia in malnourished and well-nourished Gambian children. *Pediatr Infect Dis J* 1994;**13**:975-82.
19. Johnson A, Aderele W, Osinusi K, Gbadero D, Fagbami A, Rotowa N. Acute bronchiolitis in tropical Africa: a hospital-based perspective in Ibadan, Nigeria. *Pediatr Pulmonol*. 1996;**22**:236-47.
20. Tewari A, Sen R, Mittal K, Saini R, Sen J. Lung puncture aspiration in the diagnosis of acute pneumonias. *Indian Pediatr*. 1991;**28**:647-52.
21. Misra S, Bhakoo O, Ayyagiri A, Katariya S. Clinical & bacteriological profile of neonatal pneumonia. *Indian J Med Res*. 1991;**93**:366-70.
22. George S, Bai S, Cherian A. Blood versus lung aspirate culture in pneumonia. *Indian Pediatr*. 1996;**33**:871-2.
23. Prakash J, Agarwal D, Agarwal K, Gulati A. Etiologic diagnosis of pneumonia in under five children. *Indian Pediatr*. 1996;**33**:329-31.
24. Patwari A, Bisht S, Srinivasan A, Deb M, Chattopadhyaya D. Aetiology of pneumonia in hospitalized children. *J Trop Pediatr*. 1996;**42**:15-20.
25. Gratten M, Montgomery J. The bacteriology of acute pneumonia and meningitis in children in Papua New Guinea: assumptions, facts and technical strategies. *P N G Med J*. 1991;**34**:185-98.
26. Graham S, Mtitimila E, Kamanga H, Walsh A, Hart C, Molyneux M. Clinical presentation and outcome of Pneumocystis carinii pneumonia in Malawian children. *Lancet* 2000;**355**:363-73.

27. Bakeera-Kitaka S, Musoke P, Downing R, Tumwine J. Pneumocystis carinii in children with severe pneumonia at Mulago Hospital, Uganda. *Ann Trop Paediatr* 2004;**24**:227-35.
28. Zar H, Dechaboon A, Hanslo D, Apolles P, Magnus K, Hussey G. Pneumocystis carinii pneumonia in South African children infected with human immunodeficiency virus. *Pediatr Infect Dis J* 2000;**19**:603-7.
29. Mulholland K HS, Adegbola R, Usen S, Oparaugo A, Omosigho C, Weber M, Palmer A, Schneider G, Jobe K, Lahai G, Jaffar S, Secka O, Lin K, Ethevenaux C, Greenwood B. Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine for prevention of pneumonia and meningitis in Gambian infants. *The Lancet* 1997;**349**:1191-97.
30. Klugman K, Madhi S, Huebner R, et al. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med.* 2003;**349**:1341-8.
31. Cowgill K, Ndiritu M, Nyiro J, et al. Effectiveness of Haemophilus influenzae type b Conjugate vaccine introduction into routine childhood immunization in Kenya. *JAMA* 2006;**296**:671-8.

TABLE 1: Studies on pneumonia aetiology from developing countries

Author, study design	Setting	Sample size	Inclusion criteria	Investigations	Results
Bakeera-Kitaka ²⁷ , 2004 Case series	Uganda, Teaching Referral Hospital	121	Children aged 2-60 months presenting to hospital with severe pneumonia	Sputum fluorescence microscopy	PCP prevalence: 16.5% (20 out of 121) 18/43-HIV infected 2/78-not HIV infected
Vuori-Holopainen ¹¹ , 2001 Systematic review*	Studies from all 6 continents. (Selected studies from Africa, Asia and Papua New Guinea.)	546** (aetiological agent identified in 278 cases)	Original reports on the use of lung tap in cases of childhood pneumonia described in medical literature up to 2001.	Lung tap	<i>S. Pneumoniae</i> 93/278(33%), <i>Haemophilus influenzae</i> 50/278(18%), and <i>Staphylococcus aureus</i> 78/278(26%).
Graham ²⁶ , 2000 Case series	Malawi, hospital	150	Children aged between 2 months and 5 years who were in hospital with a diagnosis of severe pneumonia (radiologically confirmed)	Blood cultures and immunofluorescence on nasopharyngeal aspirate samples used to test for PCP.	16 cases of PCP among 150 children; all cases were HIV positive. Bacterial pathogen: 21/150 cultures showed growth; <i>S.pneumoniae</i> (8) and non-typhoidal salmonellae (7). 10/ 16 children with PCP and 6/21 with bacterial pneumonia died (relative risk 2.19 [95% CI 1.0-4.7]).
Zar ²⁸ , 2000 Case series	South Africa, teaching hospital	151	HIV infected children hospitalized with pneumonia	Immunofluorescence and silver stain	PCP prevalence: 15/150 (9.9%; 95% CI 5.5 to 15.5) PCP was the AIDS-defining infection in 13 of 64 (20.3%; 95% confidence interval, 11.8 to 31.5). 1/59 children receiving prophylaxis (1.7%) developed PCP vs. 14 of 92 (15.2%) not

					taking prophylaxis [relative risk, 0.11 (0.02 to 0.82), P = 0.007].
Scott ³ , 1999 Systematic review*	N/A	2862(total of subjects in case series for children)	Studies reporting etiologic yield and complications of lung aspirate studies done in patients with clinical findings compatible with severe pneumonia	Lung puncture for lung aspirates	<i>S. Pneumoniae</i> (12%), <i>Haemophilus influenzae</i> (6%), and <i>Staphylococcus aureus</i> (15%). African studies: <i>S. pneumoniae</i> (17%). <i>H. Influenzae</i> (8%) and <i>s.aureus</i> (12%)
Shann ¹² , 1986 Systematic Review*	Studies done in developing countries (Asia, Africa, Latin America and Papua New Guinea)	1029- bacteriologic studies; 1212- viral studies	Studies on pneumonia aetiology conducted in developing countries	Lung aspirate; viral culture and serology	Bacterial infection: 640/1029 (62%) <i>H.influenzae</i> 176(27%), <i>S.peumoniae</i> 180 (27%), <i>S.aureus</i> 109(17%), others 192(29%) Viral infection: 281/1212 (23%) Viral vs. bacterial infection: 54/222(24%) vs. 160/320(50%) in 4 comparative studies

* Same patients reported in these reviews

**Total number of aspirates from Africa, Asia and Papua New Guinea