Epidemiology, aetiology and management of childhood acute community-acquired pneumonia in developing countries – A review

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Abstract
Childhood acute community-acquired pneumonia is one of the leading causes of morbidity and mortality in developing countries. In children who have not received prior antibiotic therapy, the main bacterial causes of clinical pneumonia in developing countries are *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), and the main viral cause is respiratory syncytial virus (RSV), but estimates of their relative importance vary in different settings. The only vaccines for the prevention of bacterial pneumonia (excluding vaccines for pertussis and measles) are Hib and pneumococcal conjugate vaccines (PCV). In children with human immunodeficiency virus (HIV) infection, bacterial infection remains a major cause of pneumonia mortality; however, *Pneumocystis jirovecii* and *Mycobacterium tuberculosis* are important causes of pneumonia in them. Studies of bacterial aetiology of *acute* pneumonia in severely malnourished children have implicated *Klebsiella pneumoniae*, *Staphylococcus aureus*, *S. pneumoniae*, *Escerichia coli*, and *H. influenzae*, with very few data on the role of respiratory viruses and tuberculosis. Studies of neonatal sepsis suggest that Gram-negative enteric organisms, particularly *Klebsiella* spp., and Gram-positive organisms, mainly pneumococcus, group b *Streptococcus* and *S. aureus* are causes of neonatal pneumonia. Many of the developing countries that ranked high in pneumonia mortality are preparing to introduce new pneumonia vaccines with support from Global Alliance for Vaccine and Immunization (GAVI Alliance), plan for the expansion of community-based case management and have ambitious plans for strengthening health systems. Assurance that these plans are implemented will require funding and continued public attention to pneumonia, which will help contribute to a substantial decline in childhood pneumonia deaths.

Keywords: *Children, community-acquired pneumonia, developing countries, epidemiology, aetiology, management, review.*

Résumé
La pneumonie aigue acquise dans l'enfance est la principale cause de souffrance et de mortalité dans les pays sous-développés. Les seules vaccins pour la prévention de la pneumonie bactérienne, excluant les vaccins contre la rougeole et varicelle sont les vaccins Hib et and conjugués pneumococales (VCP). Chez les enfants ayant l'infection du virus immunodéficitaire (VIH), l'infection bactérienne reste la cause majeure de la mortalité en pneumonie; Cependant, *Pneumocystis jirovecii* et *Mycobacterium tuberculosis sont les causes important de leur pneumonie*. Les études sur l'étiologie bactérienne de la pneumonie aigue chez les enfants sévèrement malnutris ont impliquées les espèces de *Klebsiella pneumoniae*, *Staphylocoque aureus*, *S. pneumoniae*, *Escherichia. coli*, et *H. influenzae*, dans leur rôle dans ces cas de virus respiratoires et tuberculose. Les études sur la septicémie néonatale suggèrent que les organismes entériques de grammes négatifs, particulièrement les espèces de *Klebsiella*, et les grammes positifs, principalement les pneumocoques, groupe de *Streptocoque et S. aureus sont les causes de la* pneumonie néonatale. Plusieurs des pays sous-développés qui sont classes ayant un taux de mortalité élevé en pneumonie se préparent à introduire de vaccines nouvelles contre la pneumonie de l'alliance GAVI, plan d'expansion des soins communautaires dans l'ambition de renforcer les systèmes de santé. L'assurance que ces plans mise en place nécessitent de financement et l'attention continue du public en pneumonie, qui contribuera à la réduction considérable des décès de pneumonie enfantine.

Introduction

Childhood pneumonia is both an important cause of morbidity and mortality in the developing countries especially sub-Saharan Africa. More than 155 million new episodes of clinical pneumonia occur in children under 5 years of age annually with about 10% of these being of sufficient severity to be life-threatening requiring hospitalization. It is estimated that up to 1.6 million under-five deaths annually are due to pneumonia accounting for 18% of the 8.8 million global childhood deaths[1] and over 70% of under-five mortality occur in south Asia and sub-Saharan Africa[2]. With the realization that the United Nations

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Assembly Millennium Development Goal 4 (MDG4), aimed at reducing under-five rate by two thirds between 1990 and 2015 be achieved without dealing with the problem ildhood pneumonia, the World Health Assembly d a resolution recognizing pneumonia as the d's leading infectious killer of children on May 010[3] and thus making pneumonia a global h priority. There are two major types of pneua: community-acquired pneumonia (CAP) and omial pneumonia. CAP, which is the focus of eview, is defined as pneumonia in a previously y child who acquired the infection outside a tal or develops the illness within 48 hours of ssion into a hospital.

itions of pneumonia

monia is defined histopathologically as an mmatory condition involving the lungs, which de the visceral pleura, connective tissue, airways, li, and vascular structures. Acute lower atory tract infection (ALRTI) is frequently used hangeably to include bronchitis, bronchiolitis, neumonia, or any combination of the three.

The World Health Organization (WHO) al definition of pneumonia relies on simple al signs, such as tachypnoea and lower chest wing (Table 1), which have been shown to be le signs of pneumonia [4] even though these are of slightly lesser sensitivity and specificity verely malnourished children than in well-shed children [5]. While these signs are priate for case management in primary care programmes where high sensitivity is tant, they are not sufficiently specific to tely estimate the burden of disease and give icacy estimates for interventions that are aimed cally at preventing bacterial pneumonia.

McIntosh defined pneumonia as presence of cute respiratory symptoms or both, plus e of parenchymal infiltrates on chest h [6]. Another similar definition of is a condition typically associated with respiratory symptoms, and evidence of ymal involvement, either by physical tion or the presence of infiltrates on chest ph.

is of pneumonia

orthy that the WHO's clinical definition of ia does not attempt to distinguish between ia and bronchiolitis, which are in fact two nditions (although with a degree of clinical p) whose prognosis and clinical features are different. Bronchiolitis tends to be viral, self-limiting, and associated with wheezing, whereas pneumonia tends to be bacterial (especially in the developing world), to have a significant mortality, and not to have associated wheezing. In sub-Saharan Africa, symptoms of pneumonia often overlap with those of malaria [7, 8]. In the past, this necessitated the recommendation that all children with respiratory signs warranting hospital admission in a malaria endemic area should be treated for both malaria and pneumonia unless blood film examination excludes malaria. With the sensitivity of current definitions of tachypnoea for diagnosing radiological pneumonia ranging from 72% to 94% , and specificities between 38% and 99%; chest indrawing sensitivities of between 46% and 78% [9], use of malaria rapid diagnostic test in their management can potentially avoid over-prescribing of malaria medications[10,11]. Physicians use auscultatory signs like bronchial breath sounds and crackles in the clinical diagnosis of pneumonia but these are not always present and inter-observer agreement regarding the presence and absence of these signs has been poor [12,13]. As a result, the diagnosis of pneumonia using auscultatory findings has been difficult to standardize. Radiography is the gold standard for the diagnosis of pneumonia, however interpretation of the radiological findings used to define pneumonia is varied. While some studies have classified only cases with alveolar consolidation as pneumonia, others have considered the presence of any pulmonary parenchymal infiltrates as constituting pneumonia. Furthermore, there is relatively poor agreement even between radiologists on the presence or absence of infiltrates in paediatric chest radiographs. This variability persists even when standard definitions and reporting forms are used. Besides this, a study of 14 malnourished children with suspected pneumonia revealed that chest radiographs predicted the post-mortem diagnosis of pneumonia with 100% specificity but only 50% sensitivity [14]. This is consistent with the finding that neutropaenic patients with pneumonia may have normal chest radiographs [15]. This observation has important implications in Africa, where the prevalence of underweight was forecasted to increase from 24.0% to 26.8%, due to increases from subregions of sub-Saharan Africa: Eastern, Middle, and Western Africa [16]. Chest radiograph is useful in making diagnosis of bacterial pneumonia (focal infiltrates) in HIV-infected children. But, chest radiographic findings may be normal, atypical or protean in pulmonary tuberculosis because of severe immunosuppresion. Despite this and due to the poor reliability of the auscultatory signs in the chest in

Table 1: Simple clinical signs for and severity classification of pneumonia in under-5s

Non-Severe Pneumonia	Cough or difficult breathing and tachypnoea* . age < 2 months ≥ 60 breaths/min . age 2 up to 12 months :≥ 50 breaths/min . age 1 up to 5 years :≥ 40 breaths/min
Severe Pneumonia	Cough or difficult breathing plus **at least one** of the following signs: . Lower chest wall indrawing; . Nasal flaring; . Grunting (in young infants).
Very Severe Pneumonia	Cough or difficult breathing plus **at least one** of the following: . Central cyanosis; . Inability to breast feed or drink, or vomiting everything; . (*convulsions, lethargy or unconsciousness*); . Severe respiratory distress.

*: *The respiratory rate is counted when the child is asleep or awake and calm.*

detecting pneumonia, chest radiography still remains the best available tool to diagnose pneumonia. Taking all these together, Cherian has delineated diagnostic spectrum of pneumonia into five; those in which diagnosis is based on: i) simple clinical signs; ii) any abnormal chest X-ray findings; iii) indirect markers; iv) lobar consolidation in chest radiographs and v) positive bacterial culture. Degree of sensitivity and specificity in the five groups shows inverse relationship (Figure 1).

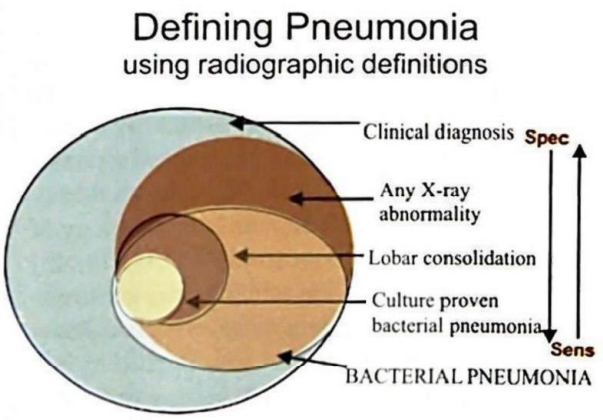
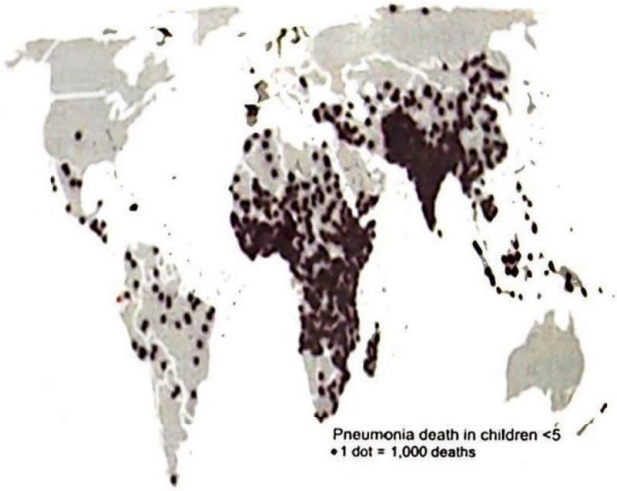


Fig.1: The diagnostic spectrum of pneumonia and associated sensitivity (sens.) and specificity (spec.)

Epidemiology

Incidence

The burden of pneumonia is on under-5s especially 2 years and younger. Every year there are 156 million new episodes of pneumonia in under-5s worldwide,



Source: GAVI Alliance

Fig. 2: Pneumonia deaths in the world.

of which 151 million episodes are in the developing world and about 35 million episodes in Africa [17, 18]. This translates into an incidence of 0.29 episodes per child-year (e/cy) in developing countries, 0.33 e/cy in Africa and 0.34 e/cy in Nigeria. The incidence is 0.05 e/cy in developed countries, which is a sixth of that in the developing countries [18]. Generally, about 10% (range 7-13%) of community cases is severe enough to require hospitalization [18].

Mortality

Worldwide, pneumonia is the number one killer of under-5s [19]. Nearly 1.6 million children under the age of 5 years die of pneumonia annually which is one child every 20 seconds and 4,300 young lives lost every day [20]. About 98% of these children who die of pneumonia live in developing countries [21]; and 70% are in Africa and south-east Asia [19] (Figure 2). For every 1 child that dies of pneumonia in a developed country, more than 2000 children die in developing countries [21]. According to 2008 estimates, about 177,000 children under the age of five years died of pneumonia in Nigeria [20], which was the highest in Africa, second highest overall in the world [20], and third highest cause of the 1 million deaths in Nigerian under-5s, and indeed the commonest cause of vaccine preventable diseases in Nigeria [20].

Seasonality

The association between exposure to cold weather and pneumonia has remained unclear. It is certain that bacteria and viruses, and in a few cases non-bacterial and non-viral agents, and not cold or wet weather, cause pneumonia. Viruses which cause

ALRTI express seasonal variation in occurrence [22]. The rate of colonization with respiratory pathogens also increases in midwinter [23]. The seasonality of respiratory syncytial virus (RSV) infection in tropical and developing countries is of relevance to Nigeria and other tropical African countries. RSV infection is seasonal in most countries; outbreaks occur most frequently in the cold season in areas with temperate and Mediterranean climates and in the wet season in tropical countries with seasonal rainfall [24]. Similar data on seasonality of influenza virus infections has major implications on seasonal immunization with influenza vaccines. Seasonal variation is also seen with bacterial pathogens. The incidence of invasive pneumococcal diseases has been reported to increase during colder months in temperate regions [25, 26]. Colonization with a virus predisposes to increased bacterial infection; a relationship already established between influenza A and invasive pneumococcal infection [27]. The association between respiratory viral infections and bacterial pneumonia is not limited to influenza alone, but also to other respiratory viral infections. This is also evidenced by the impact of pneumococcal vaccines on hospitalization from virus associated pneumonia [28]. The seasonal variation in infectious diseases may result from variation in the susceptibility of the human host [29]. The tendency for many people to stay indoor during the cold seasons is associated with an increased risk of developing pneumonia. Crowding favours the spread of respiratory pathogens. In northern latitudes, the cooling of weather in autumn forces people to spend more time indoors. On the other hand, in tropical weather respiratory infections are common during rainy seasons [30]. The bad weather, but not necessarily so cold, gathers people together. Inspiration of cold air causes a decrease in the temperature of the respiratory epithelium and hence decreases mucociliary clearance and the local immune responses of the airway [31].

It has been established that prolonged exposure to extremely cold temperature, a form of cold stress can lead to hypothermia, which causes alterations in the systemic and local defences against respiratory infections, favouring the infection by inhalation of pathogens normally present in the oropharynx [32].

Risk factors

Risk factors for the development of pneumonia have been categorised by Rudan *et al* [18] into: definite (most evidence consistently pointing to the role of the risk factor); likely (most evidence consistently pointing to the role, but with some opposing findings; or scarce but consistent evidence of the role); and possible (with sporadic and inconsistent reports of the role in some contexts). These risk factors are related to the host or the environment (Table 2).

Table 2: Risk factors related to the host and the environment that a[illegible]he incidence of childhood clinical pneumonia in comm[illegible] in developing countries (from Rudan *et al* [18])

Definite Risk Factors	
(most evidence consistently pointing to the role of the risk factor)	• Malnutrition (weight-for-age z-score < -2) • Low birth weight (<2500 g) • Non-exclusive breastfeeding (during first 4 months of life) • Lack of measles immunization (within first 12 months of life) • Indoor air pollution • Crowding
Likely [illegible]sk Factors	
(most evidence consistently pointing to the role, but with some opposing findings; or scarce but consistent findings of the role)	• Parental smoking • Zinc deficiency • Mother's experience as a caregiver • Concomitant disease (diarrhoea, heart disease, asthma)
Possible Risk Factors	
(sporadic and inconsistent reports of the role in some contexts)	• Mother's education • Day-care attendance • Rainfall (humidity) • High altitude (cold air) • Vitamin A deficiency • Birth order • Outdoor air pollution

Aetiology

Methods for pathogens detection

Pathogens of childhood CAP include viruses, bacteria, mycobacteria, and fungi. Identification of these pathogens involves microscopy and/or culture of, as well as viral and mycological studies of blood, percutaneous lung aspirates, nasopharyngeal aspirates and i[illegible]ced sputum [24, 26, 33–56]. The sensitivity of blood culture in the determination of aetiology of bacterial pneumonia is low (10 -30%) [34, 35, 43] and may not always provide reliable information to guide antibiotic management of severe pneumonia [43]. Reasons adduced for this low sensitivity are non-bacteraemic pneumonia, prior antibiotic treatment, and the causative organisms hiding within polymorphs. Although specificity of blood culture is high, in about 7% of cases, isolates from blood and lung [illegible]te are dissimilar [43]. Attempts to increase patho[illegible] yield from blood include use of polymerase chain reaction (PCR) on blood culture supernatant; and in one series sensitivity and specificity of *S. pneumoniae* and Hib yield from blood culture supernatant was as high as 100% and 99%, respectively [57-59]. Apart from its expensive cost, a systematic review and meta-analysis of this

molecular-based method for the diagnosis of bacterial infections in blood showed that the currently available methods for PCR with blood samples for the diagnosis of invasive pneumococcal disease lack the sensitivity and specificity necessary for clinical practice[60]. However, a recently reported study from Malawi showed that in a select group of African children, lung aspirate PCR significantly improved diagnostic yield [61].

The impact of prior antibiotic exposure on blood culture yield can be minimized by the use of the Bactec culture system with culture bottles containing resins which are an antibiotic-removing device. Automated blood culture methods such as the BACTEC (BACT/ALERT) culture system, can detect bacterial growth at a concentration of 1-2 colony forming units/ml (cfu/ml), within 24 hours of incubation [62].

The 'gold standard' for diagnosis of pathogens causing CAP is culture of lung aspirate and with this method there is increased diagnostic yield of *M. tuberculosis* [35]. Although culture of lung aspirates gives a far higher yield of pathogenic bacteria than blood culture [35, 44] the technique is limited to children with lobar pneumonia and may neither be suitable for routine use nor in children with bronchopneumonia[35].

Induced sputum is useful in the diagnosis of mycobacterium tuberculosis [35] and *P. jirovecii* [38, 41] in children, and is of no diagnostic value for the common bacterial respiratory pathogens because the sputum is invariably contaminated with bacterial commensals in the nasopharynx. Indirect markers of bacterial cause are not specific enough to distinguish between carriage of *S. pneumoniae* and *H. influenzae*, which is usual for children in developing countries, and invasive disease [63].

Nasopharyngeal aspirates are used for identification of viruses [24, 35, 38, 42] and *P. jirovecii* [33, 41]. Rapid diagnostic tests (indirect immunofluorescence, enzyme-linked immunosorbent assay, polymerase chain reaction) and viral culture on nasopharyngeal aspirates as well as viral serology in paired serum samples are the standard techniques in viral aetiology of pneumonia [24, 64].

The use of vaccine probe, a new epidemiological tool, has provided us with the opportunity to define indirectly the burden of vaccine-preventable pneumonia, which is presumed to be a minimum estimate of the burden of pneumonia due to the organism against which the vaccine is directed[27, 65].

Aetiological pathogens

The two commonest bacteria from bacteriological analysis of lung aspirates and blood cultures from children (3 - 59 months) who have not received prior antibiotic therapy are *S. pneumoniae* (30–50% of pneumonia cases) and *H. influenzae* type b (Hib; 10–30% of cases)[27,28,33-35, 45-47]. The routine immunisation of children against Hib in some developing countries has decreased the incidence of pneumonia due to this bacterium, although non-typeable strains are still responsible for a small proportion of pneumonia. Other bacterial pathogens of pneumonia are S. *aureus, Klebsiella pneumoniae,* non-typeable *H. influenzae* (NTHI), and non-typhoid *Salmonella* spp. NTHI was found to be an important pathogen in a lung aspirate study from Papua New Guinea [47], and was a common blood culture isolate from studies in Pakistan [49, 66], whereas in a lung aspirate study from the Gambia [35], and in most blood culture-based studies, Hib was the main type of *H. influenzae* identified. In a post-introduction of Hib conjugate vaccine surveillance study in South Africa during the period 1999 – 2004, NTHI was a significant blood culture isolate in under-5s, but it was not indicated if they were pneumonia cases [67]. The controversy that surrounds the importance of *S. aureus* in the aetiology of CAP was lessened by a multicentre study in seven developing countries which found *S. aureus* in 47 of the 112 (42%) of cases in which a bacterium was identified, making it the second largest cause[50]. In Malawi, non-typhoid *Salmonella* spp. has been implicated in cases with radiological pneumonia [51], but the role of this organism is still unclear, as blood-culture studies may have identified children with bacteraemia only [52].

The role of Chlamydia and *Mycoplasma pneumoniae* as important causes of under-5 childhood pneumonia in developing countries remains unclear [35, 45, 68, 69]. Other organisms, such as *Pseudomonas* spp., and *Escherichia coli*, also cause pneumonia.

RSV is the commonest viral agent of ALRTI, being identified in 15–40% of pneumonia or bronchiolitis cases admitted to hospital in children in developing countries [35, 63, 70-72]. In small infants, pneumonia and acute bronchiolitis are common and the features overlap considerably. This similarity may not be unrelated to the proximity of the anatomical sites that are inflamed in both illnesses. Acute bronchiolitis is inflammation of the bronchioles, the smallest air passages of the lungs, whereas in pneumonia, there is alveolar inflammation; the distance between a bronchiole and an alveolus is close.

Other pathogenic viruses implicated in the causation of childhood CAP are influenza A and B, parainfluenza and adenovirus [24, 63, 72].

In the last decade, development of molecular diagnostics has led to discovery of new viruses which hitherto were unknown because of failure to grow in tissue culture. These viruses are human metapneumovirus (hMPV) [73,74] human coronavirus types[75,76], human bocavirus (HBoV)[77], and human polyomaviruses [78,79]. Breakthroughs in understanding their role in causation of pneumonia, particularly in young children have been provided recently [80,81]. Human rhinovirus infection is becoming increasingly important as a common cause of viral pneumonia, and in a study in Brazil it constituted the commonest single viral agent of pneumonia [82]. Primary respiratory infection by viruses increases the risk of secondary bacterial pneumonia and viral/bacterial co-infection is a common finding in young children with pneumonia in developing countries (approximately 20–30% of episodes)[26,45,49].

The spectrum of pathogens causing pneumonia in HIV-1 infected children is similar to that in HIV-1 uninfected children, except that *S.aureus*, Gram-negative bacteria, *P. jirovecii*, cytomegalovirus (CMV) co-infection with *P. jirovecii* pneumonia (PcP) and *M. tuberculosis* are important causes of pneumonia in them [27,33,36-39,40-42,83]. However, previous data for CMV in HIV-1 related respiratory infections in children in the United Kingdom [84] and adults in the United States [85] have been contradictory. HIV-exposed, negative children have an increased risk of infection with opportunistic pathogens than HIV-1 unexposed children.

Studies of bacterial aetiology of *acute* pneumonia in severely malnourished children have implicated *K. pneumoniae*, *S. aureus*, *S. pneumoniae*, *E. coli*, and *H. influenzae*, with very few data on the role of respiratory viruses and tuberculosis [86]. The relative role of pneumococcus and Hib in malnourished children differed in different regions of developing countries even before the introduction of PCV and Hib conjugate vaccines [35, 44, 50, 54, 56].

In the past 3 decades, percutaneous lung and blood culture studies of the aetiology of community-acquired pneumonia in southern and central Nigeria reported *S. aureus* and *Klebsiella* species as common causes [54-56, 87]. Various reasons have been suggested for the underreporting of cases of pneumococcus and Hib infection, including the use of antibiotics before medical consultation, inclusion of malnourished children in studies, and use of human blood for preparation of blood agar. Malnourished children, especially those with oedematous malnutrition, are immunocompromised and thus are susceptible to infection with *S. aureus* and Gram-negative bacilli [88]. The use of human blood in the preparation of blood agar at the University College Hospital (UCH), Ibadan in the past was a contributory factor to the low isolation rate of these fastidious bacteria (UCH, personal communication). The human blood that was used most likely contained antibiotics, given the high rate of antibiotic misuse.

In a recent study at the University College Hospital (UCH), Ibadan, sheep blood was used. Using blood culture 44 cases of pneumonia were aetiologically related to *S. aureus*, but it is highly likely that many of the isolates were coagulase-negative *Staphylococcus* and thus were contaminants. This view is supported by the finding of poor correlation (5.6%) between identification of *S. aureus* at the UCH and identification at a reference laboratory, the Medical Research Council (MRC) Laboratories in The Gambia [89]. The dissimilarity in the results from the two centres was due to use of different confirmatory tests. The UCH, Ibadan used coagulase test based on ability of *S. aureus* to convert fibrinogen in plasma to fibrin clot, which gives agglutination reaction either on the slide (free) or in a tube (bound). Whereas, MRC, The Gambia used rapid commercial staphaurex (Biomerieux) - latex particles coated with fibrinogen, immunoglobulin G and protein A; it gives agglutination reaction with *S. aureus* and comes with both positive and negative controls.

Case management of childhood pneumonia

Standard case management strategy was developed by WHO in the 1980s and was later incorporated in the 1990s into the Integrated Management of Childhood Illness guidelines which include primary care (community-based case management) and hospital-based case management. Basic needs for effective case management are: evidence-based training, facilitated referral, antibiotics and oxygen.

The basis for the community-based case management strategy was that a trained community health worker could correctly identify cases of children with pneumonia by the use of simple clinical signs such as respiratory rate and chest indrawing[90]. The finding that *S. pneumoniae* and *H. influenzae* cause over 50% of pneumonia deaths [90], as well as the realization that access to health facilities remains

Table 3: Antibiotic treatment of community-acquired pneumonia

Severity of pneumonia	First line antibiotic	Second line antibiotic	Monitoring
Very severe	Ampicillin 40 mg/kg or benzyl penicillin 50,000 units per kg im/iv every 6 hours for at leas 5 days.Gentamicin: 7.5 mg/kg im/iv once a day for at least 5 days.	If no improvement within 48 hours, switch to ceftriaxone course for 3 weeks (80 mg/kg iv once daily) OR gentamicin plus cloxacillin	3 hourly nursing observations.Doctor's review at least twice a day.
Very severe with HIV or suspected HIV	High-dose cotrimoxazole (5 mg/kg of trimethoprim and 25 mg/kg of sulfametho -xazole) IV every 6 hours or orally 6 hourly a day) for 3 weeks. Additionally: Ampicillin plus gentamicin for 10 days.	If no improvement within 48 hours, switch to ceftriaxone (80 mg/kg iv once daily) OR gentamicin plus cloxacillin, as above.	As above
Severe	Oral amoxicillin at least 40mg/ kg dose twice a day for 5 days.	If no improvement within 48 hours or deteriorates: Admit to a hospital. Look for complications such as pneumothorax or empyema and treat accordingly. If no apparent complications, switch to ampicillin 40 mg/kg or benzyl penicillin 50,000 units per kg IM/IV every 6 hours for at least 5 days Gentamicin:7.5mg/kg im/iv once a day for at least 5 days.	6 hourly nursing observations.Doctor's review once a day.
Severe with HIV or suspected HIV	Admit. IV ampicillin/ penicillin plus gentamicin or oral amoxicillin plus gentamicin. Treat for *P. jirovecii* with intravenous cotrimoxazole. Give oxygen if signs of hypoxaemia.	If not improving within 48 hours change to second-line antibiotic: ceftriaxone.	3 hourly nursing observations.Doctor's review at least twice a day.
Non-severe	Low HIV prevalence, give amoxicillin for 3 days with at least 40 mg/kg/dose two times daily for 3 days. High HIV settings, give amoxicillin at least 40 mg/kg/dose two times daily for 5 days.	Admit to hospital for treatment as severe pneumonia.	

iv = intravenous; im = intramuscular

low in many developing countries and children, especially those from poorer families are treated at home, through the informal sector or by traditional healers makes this strategy highly relevant. The case management performed includes classifying respiratory infections based on respiratory rates and lower chest indrawing, treating non-severe pneumonia with antibiotics, and referring severe pneumonia cases, where possible.

Community-based implementation of the WHO ARI case-management strategy reduced pneumonia-specific mortality by 35–40% [91]. However, implementation of the case-management strategy remains a challenge in resource-limited settings that are endemic for HIV, malnutrition, tuberculosis or malaria. In sub-Saharan Africa, symptoms of

pneumonia often overlap with those of malaria [7,8], and *Plasmodium falciparum* malaria can be rapidly fatal in children if untreated. For this reason, any febrile child in a high-risk area should be treated with an effective antimalarial whatever the alternative or co-morbid conditions. Other challenges of the community-based management of pneumonia are increasing rates of antibiotic resistance and potential changes in aetiology of pneumonia as Hib and PCV vaccines become more widely available by 2015 provided guidelines for management of children with pneumonia and HIV in resource-limited settings(Appendix II). These are summarised in table 3. Only cases of very severe pneumonia as well as cases of severe and non-severe pneumonia that failed treatment are admitted into a hospital for 2nd line antibiotics usually parenteral antibiotics. Some aspects of antibiotic treatment are different in children who are HIV positive or in whom HIV is suspected. Although the pneumonia in many of these children

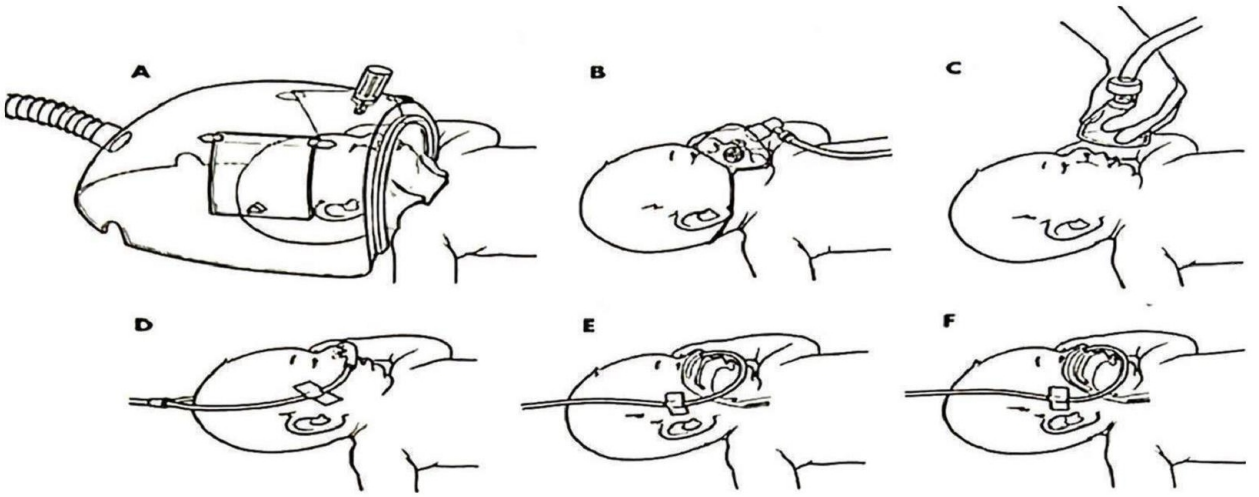


Fig.3: Methods of oxygen delivery: A, head box; B, face mask; C, funnel; D, nasal prongs(cannula); E, nasal catheter and F, nasopharyngeal catheter.

(Adegbola RA, personal communication) as well as increased prevalence of HIV. Hence, a change in the aetiological spectrum of pneumonia is expected from what was determined since the large aetiological studies cited in this paper were conducted. It is highly relevant to emphasize the need for studies to monitor and study these changes. The Pneumonia Etiology Research for Child Health (PERCH) project (http://www.jhsph.edu/ivac/perch.html) is attempting to do so. Briefly, PERCH project is a multi-country case-control study designed to determine the aetiology of severe and very severe pneumonia in hospitalized under-5 children. It aims to produce highly rigorous, representative data using state-of-the-art diagnostics and by applying a carefully standardized clinical protocol across all sites. The seven PERCH sites are in Africa (Johannesburg, South Africa; Lusaka, Zambia; Kilifi, Kenya; Basse, The Gambia and Bamako, Mali) and Asia (Sa Kaeo and Nakhon Phanom, in Thailand and Dhaka, Bangladesh).

The earlier recommendations for the antibiotic treatment of pneumonia in under-5s in the resource-limited countries [92] were recently revised by WHO on the basis of evidence from studies comparing antibiotic treatment for pneumonia (Appendix I) and has the same aetiology as in children without HIV, pneumocystis pneumonia (PcP) often at the age of 4–6 months is an important additional diagnosis which must be treated when present.

Rational use of supplemental oxygen

Hypoxaemia is a major complication and cause of deterioration in pneumonia and is associated with a significantly increased mortality risk. Oxygen is given to all children with very severe pneumonia. WHO-recommended treatment of severe pneumonia includes oxygen therapy where oxygen saturation is less than 90% (where pulse oximetry is available). Although moderately expensive, oximetry may be cost-effective, because of potential cost savings by more rational use of oxygen.

Oxygen can be delivered with nasal prongs, a nasal catheter, or a nasopharyngeal catheter (Figure 3). The maximum fractional concentration of inspired oxygen (F_IO_2) delivered by nasal prongs is 28-35% except in small infants when higher concentrations may be achieved. With nasal prongs oxygen flows of 0.5–1 l/min are required in children less than 2 months old and 2-3 l/min in children aged 2 montns-5 years. The nasal prongs should be properly applied to

prevent it from slipping away from the nostrils. Nasal catheter can deliver a slightly higher maximum F_IO_2 than nasal prongs (35-40%), however it can get blocked. Nasopharyngeal catheters require the lowest flow rate to achieve a given oxygen concentration in the airways, and infants under 2 months can usually be treated with 0.5 l/min and infants up to 1 year with 1 l/min. However, this advantage is completely offset by the followings: humidification of oxygen is mandatory, the catheter can easily block and other serious complications like gastric distension, airway obstruction and apnoea can occur, necessitating continuous skilled nursing to prevent these complications. On the balance, use of nasal prongs is considered the best method for delivering oxygen to young infants. Face masks are not recommended because much higher flow rate of 6-10 l/min is required to deliver 28% - 65% oxygen.

Where pulse oximetry is not available oxygen is given until the simple clinical signs of hypoxia (such as severe lower chest wall indrawing or breathing rate of ≥70/minute) are no longer present. Where pulse oximetry is available a trial period without oxygen is carried out each day in stable children. Oxygen is discontinued if the saturation remains stable above 90%. Nurses should check every 3 hours that the catheter or prongs are not blocked with mucus and are in the correct place and that all connections are secure. The two main sources of oxygen are cylinders and oxygen concentrators.

Supportive care

Supportive care is also important in the treatment of pneumonia. If the child's fever is ≥39 °C which appears to be causing distress, paracetamol is given. If wheeze is present, a rapid-acting bronchodilator such as nebulized salbutamol is given. Through gentle suction any thick secretions in the throat, which the child cannot clear are removed. Breastfeeding and oral fluids should be encouraged and if the child cannot drink, insert a nasogastric tube for feeding in frequent small amounts. If oxygen is given at the same time as nasogastric fluids, pass both tubes through the same nostril. Encourage the child to eat as soon as food can be taken.

Global action plan for prevention and control of pneumonia

Effective interventions exist for prevention and treatment of pneumonia in the developing countries. But, a determined effort to make effective combined use of these interventions at the country level has been missing. The challenges in the management of CAP in the developing countries are due to limited access to care, increasing antibiotic resistance, often insufficient treatment as well as prevalent sickle cell disease and HIV disease. To this end the WHO and UNICEF developed a Global Action Plan For Prevention and Control of Pneumonia (GAPP) in 2009. This consists of a simple three-pronged solution - protect, prevent, and treat - which has the potential to save more than a million children from dying of pneumonia every year globally (Table 4).

Table 4: Global Action Plan For Prevention and Control of Pneumonia (GAPP)

Protect children by	• Exclusive breastfeeding • Adequate nutrition • Reducing indoor air pollution • Hand washing
Prevent pneumonia by	• Vaccinations against pneumococcus and HiB, and also against measles and pertussis • Zinc supplementation
Treat pneumonia by	• Early detection • Appropriate antibiotics • Oxygen therapy

One of the strategies which helps protect children from pneumonia is exclusive breastfeeding during the first 6 months of life [93]. In the developing world, breastfeeding is nearly universal, with most children being breastfed for some time. However, percentages for exclusive breastfeeding durir g the first 6 months continue to be low across the developing world.

In Nigeria, only 20% of babies are exclusively breastfed, this needs to be improved [94]. Other strategies which help protect include: good nutrition, hand washing, reduced indoor air pollution [93], vitamin A supplementation and zinc intake, and increased immunization rates with vaccines that help prevent children from developing infections such as measles and pertussis.

The prevention of childhood pneumonia has been emphasized as being critical in order to achieve the MDG 4, to reduce by two-thirds the mortality rate among children under 5. Vaccination programmes in countries where children die of pneumonia should include immunizations that prevent the major causes of pneumonia deaths. Pertussis and measles immunizations are already in Nigerian national programmes. Vaccines against pneumococcus and Hib, estimated to cause more than 50% of deadly pneumonia should be added as soon as possible.

With help from GAVI Alliance, many countries in Africa now provide or will soon provide the Hib vaccine. A pneumococcal conjugate vaccine has

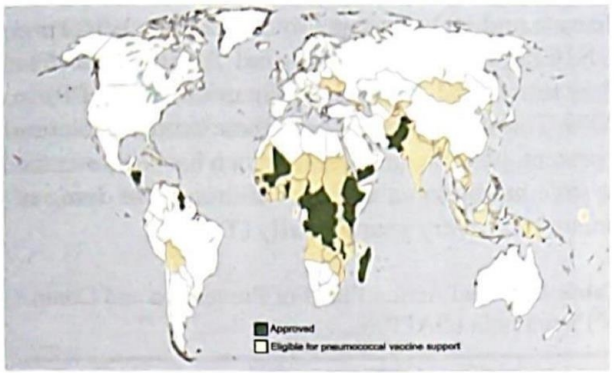


Fig. 4: Map of countries approved for GAVI's pneumococcal vaccine support

already been introduced in Rwanda, The Gambia, South Africa and Kenya. With the advent of the Advance Market Commitment (AMC), more low income countries like Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Guyana, Honduras, Mali, Nicaragua, Sierra Leone, Yemen and Burundi now have access to this new generation vaccine (Figure 4). The Nigerian government is striving to include Hib and pneumococcal vaccines into the national immunization program with GAVI's support [95]. However, it is worth stating that the current levels of immunization coverage in Nigeria (specifically in the northern states) will not result in the desired impact. This is especially true since pneumonia mortality is likely to be highest in those who do not have access to immunization services. Hence, the need for Nigeria to strive towards a more equitable coverage with vaccines, which is currently a problem in the country.

The planned introduction of Hib vaccine and PCV into the Nigerian national immunization programme is also an opportunity to scale up other interventions for pneumonia prevention and treatment, as proposed in GAPP. Nigeria recently participated in a WHO sponsored workshop and developed a list of priority activities to implement the GAPP strategies (T. Cherian, personal communication). This review paper is an additional effort to spur the Ministry of Health at all its levels (Federal, State and Local Government Area) to implement the planned activities.

Both the 10-valent and 13-valent pneumococcal vaccines provide good coverage of circulating serotypes in Africa, and the introduction of either or both should be enthusiastically received. Replacement of the 7-valent pneumococcal conjugate vaccine (PCV) with either a 10-valent (Synflorix™) or 13-valent PCV(Prevenar™) is desired, to increase coverage against circulating serotypes from ~66% to >82%. The decision on which vaccine is favourable may depend on the effect of Synflorix™ on acute otitis media (AOM), but currently there is a lack of data on AOM burden of disease in Africa. Choice of vaccine will ultimately depend on numerous factors in addition to vaccine efficacy, such as vaccine cost and political will [96].

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Appendix I

WHO RECOMMENDATION FOR TREATMENT OF COUGH AND DIFFICULT IN BREATHING

Treatment of non-severe pneumonia with wheeze

Children with non-severe pneumonia (fast breathing with no chest indrawing or danger sign) with a wheeze but with no fever (< temperature 38°C) the use of antibiotics is not recom-mended as the cause is most likely to be viral.

(Strong recommendation, low quality evidence)

Remarks

This recommendation is applicable only in situations where the health workers are able to assess "wheeze". The panel observed that there is evidence that WHO criteria for diagnosing pneumonia performs poorly in children with wheeze; that the addition of fever to WHO criteria improves diagnostic accuracy in this group of children; and that children with wheeze and no fever are very unlikely to have bacterial pneumonia.

Treatment of non-severe pneumonia with no wheeze

Children with non-severe pneumonia (fast breathing with no chest indrawing or danger sign) should be treated with oral amoxicillin.

- In low HIV prevalence, give amoxicillin for 3 days with at least 40 mg/kg/dose two times daily for 3 days.
- In high HIV settings, give amoxicillin at least 40 mg/kg/dose two times daily treatment for 5 days.

(Weak recommendation, moderate quality evidence)

Remarks

The panel noted that most of the RCTs were conducted in Asia, and mostly in low HIV settings. Amoxicillin was recommended based on values and preferences since dispersible amoxicillin is becoming more available and the cost is reducing. However there was concern about the second line treatment, panel proposed referral as one option in case of treatment failure with amoxicillin.

The panel also clarified that the moderate quality evidence relates to comparisons of the duration of the two antibiotic regimens of amoxicillin 3 versus 5 days which showed that they were not different in terms of cure and clinical failure rates.

Antibiotics for severe pneumonia

Children aged 2-59 months with severe pneumonia (chest in-drawing) should be treated with oral amoxicillin at least 40 mg/kg/dose twice a day for 5 days.

- In HIV/AIDS infected children, specific guidelines for treatment of severe pneumonia in the context of HIV should be followed.

(Strong recommendation, moderate quality evidence)

Remarks

Although this recommendation may be applicable to case management at the community or outpatients, its implementation should be guided by the clinical context and setting. However, this recommendation will not apply in HIV/AIDS infected children for whom clinicians should follow the current HIV specific guidelines.

Antibiotics for very severe pneumonia

Treat children aged 2-59 months with very severe pneumonia with parenteral ampicillin (or penicillin) and gentamicin.

- Ampicillin or Benzyl penicillin: Ampicillin 40 mg/kg or Benzyl penicillin 50,000 units per kg IM/IV every 6 hours for at least 5 days
- Gentamicin: 7.5 mg/kg IM/IV once a day for at least 5 days.

(Strong recommendation, moderate quality evidence)

Remarks

In making this recommendation, the panel noted that there is good evidence against the continued use of chloramphenicol and major concerns about future supplies. It also noted that there was poor evidence in favour of use of ampicillin and gentamicin. Although there was no data on the use of ceftriaxone, the panel recognized the need to include ceftriaxone as a second line treatment for children with very severe pneumonia especially for hospital care.

Appendix II

WHO RECOMMENDATION FOR TREATMENT OF COUGH AND DIFFICULT IN BREATHING IN HIGH HIV PREVALENCE SETTING

Non-severe pneumonia (0–5 years)

- Oral amoxicillin as first-line antibiotic. Oral cotrimoxazole is also recommended, but should ideally not be used routinely as this will encourage

nce and diminish its effectiveness against *P. cii*.

ular follow-up to monitor progress.

e pneumonia (2–11 months)

pitalize and administer intravenous antibiotic: illin/penicillin plus gentamicin or oral cillin plus gentamicin.

for *P. jirovecii* with intravenous cotrimoxazole.

t improving within 72 h change to second-line otic: ceftriaxone.

- Give oxygen if signs of hypoxaemia.

Severe pneumonia (12–59 months)

- Hospitalize and administer intravenous antibiotic: ampicillin/penicillin plus gentamicin or oral amoxicillin plus gentamicin.
- Treat for *P. jirovecii* if clinically indicated.
- If not improving within 72 hr change to second line antibiotic: ceftriaxone.
- Give oxygen if signs of hypoxaemia.