Childhood pneumonia in developing countries

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Introduction

Pneumonia is a leading cause of death among children worldwide; however, in developing countries the greatest burden of the disease is among the under-5s. This review article details the aetiology, clinical features, investigations, diagnosis, complications, treatment, and other forms of management of pneumonia. The prevention of pneumonia is discussed and the future prospects for prevention using vaccines is highlighted. The impact of ensuring that the disease is recognised early and adequate treatment given at the primary care level is emphasised as this can dramatically reduce the mortality and morbidity associated with pneumonia.

The term pneumonia refers to a pathogen-initiated acute inflammation of the lower respiratory tract, characterised by inflammation of the lung parenchyma (i.e. the respiratory unit comprising the alveoli, alveolar ducts, and the interstitial tissues). In a recent comprehensive discourse on the subject, Stein and Marostica defined pneumonia as 'Inflammation of the lung parenchyma due to an infectious agent(s) causing a response that results in damage to the lung tissue; subsequent resolution may be complete or partial.'[1] On a general note, the pneumonia can be classified (based on the origin) as either 'community acquired' (when the presumed pathogen is acquired outside the health facility), or 'healthcare associated' when the antecedents of the disease and aetiological agent(s) can be traced to a health facility or hospital. In addition, with the recent advent of HIV/AIDs, and the frequent, but fairly distinctive epidemiologic risk factors and pathogens of pneumonia associated with the disease, a new addition to the current nosology of pneumonia has been pneumonia in the immunocompromised host. It can also be defined based on aetiology – viral, bacterial; and on an anatomical basis – lobar or bronchopneumonia.[2]

In developing countries (Nigeria inclusive), the operational definition of pneumonia adopted by WHO is based on the presence of (easily recognisable) clinical parameters like fast breathing (tachypnoea) or chest indrawing/retraction, in a child with cough and/or difficult breathing of more than 28 days. The clinical value of this diagnostic strategy (in which the focal clinical signs are tachypnoea and chest indrawing) is underscored by the reported sensitivity and specificity of 74% and 67%.[3] An equally noteworthy operational definition peculiar to the 'high pneumonia incidence' countries of the developing world is the preferred use of the term 'acute lower respiratory infections (ALRI)' as a synonym for pneumonia,[4] partly in view of the overwhelming proportion (over 75%) of ALRI attributable to pneumonia, the understandable difficulties in accomplishing the prerequisites of the microbiologic or radiologic diagnosis, as well as the significant symptom overlap between pneumonia and the less common ALRI syndromes.

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Epidemiology: morbidity and mortality burden, and risk factors

Incidence data of the total paediatric ARI burden (three to eight episodes per child per year in urban communities and one to three episodes in rural communities with most of these being self-limiting viral upper respiratory infection (URI), the duration of illness, outpatient burden, and, to a large extent, the frequency of severe ALRI-related admissions in children are similar between the developed countries and the resource-poor nations; however, a tremendous disparity exists between the two categories of nations with respect to pneumonia-related deaths.[5] The incidence of pneumonia in the Western world (Europe and North America), has been estimated to be approx. 36/1000/year. Furthermore, while the pneumonia-related mortality in the Western world remains relatively low, global mortality data ascribed 3–4 million of the 12 million deaths in under-5s to severe ARI, with pneumonia accounting for more than 75% (WHO, 1992). A corresponding 2004/06 UNICEF/WHO data however suggested a significant reduction (from 4 to 1.9 million) of the global mortality burden of childhood pneumonia (WHO, 2006). Pneumonia accounted for approximately one-fifth (19%) of the 2 million deaths with 90% of these occurring in the developing world; 50% of these deaths occur in Africa alone.

The explanation for the disproportionately higher share of the global mortality burden of pneumonia in Africa has been hinged partly on the reportedly higher incidence of bacterial aetiology of the disease, and as

suggested by the findings of the comprehensive study, the African regional disease severity may also be associated with the possible role of multiple pathogens.[6,7] Other possible reasons include inadequate health education (of care givers) regarding early home recognition of signs of severe disease, indications for seeking facility consultation, and simple homecare remedies for a child with cough and difficult breathing. Several studies have also shown that the prevalence of several risk factors of severe ALRI/pneumonia is higher in the poor-resource tropical countries.[8–11] Perhaps the most dominant of these is underlying malnutrition,[7,12] but others include exposure to environmental pollutants especially the combustive products of domestic biomass burning, particularly from domestic cooking with firewood,[12] poor immunisation coverage, and the related higher prevalence of ALRI-associated but vaccine-preventable diseases (VPD) – like measles, pertussis, diphtheria, and *Haemophilus influenzae* (Hib), adverse socioeconomic variables like poor parental income/literacy, overcrowding and man-made or natural disasters with consequent living in squatter/refugee conditions. Figure 1 summarises the major predisposing risk factors of severe ALRI in children, and those that portend a fatal outcome.

Aetiological agents (pathogens)

The spectrum of possible pathogens of acute pneumonia varies widely. Lung aspirate studies from several countries have shown that bacterial agents account for over 60% of pneumonias in the developing world, with *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Staphylococcus aureus* constituting the top three.[13–15] Reports from some urban third world communities of tropical Africa, Latin America, and the Asian sub-continent have ascribed a greater aetiologic role to *Staph aureus* and other necrotising pathogens.[7,9,16,17] Blood culture-generated bacteriological data from urban Nigerian communities showed that *Staph aureus* and Klebsiella species constitute the local dominant pathogens of community-acquired pneumonia (CAP) in Nigerian children.[7,9,17,18] The Gram-negative enterobacteriacae like *Klebsiella*, *Escherichia coli*, *Proteus* and *Pseudomonas* species were reportedly common in neonates and children with measles, malnutrition and other immunocompromised states.[2,19–21] Fungal agents like *Candida*, *Aspergillus*, *Cryptococcus*, *Histoplasma*, *Norcardia* species and *Pneumocystis jiroveci* also account for a significant proportion of non-bacterial pneumonia in the immunocompromised host.[19,21] It is also noteworthy that *Mycobacterium tuberculosis* does cause pneumonia, but frequently with a chronic course, sometimes with acute presentation.

Finally, it is also noteworthy that whereas bacterial agents remain the dominant pathogens of severe (childhood) pneumonia in the developing world, the aetiological importance of viral pathogens, sometimes as multiple agents, was highlighted in some earlier reports emanating from Asia and sub-Saharan Africa.[6,7,22] With respiratory syncytial virus (RSV) and parainfluenza (PIV) constituting the top two, the spectrum of the viral agents and their aetiological ranking appeared comparable to those reported by workers in the developed world.[23]

The more common causes of pneumonia (bacterial and non-bacterial) in otherwise healthy children are summarised in Figure 2.

* **Demographic**: age and age-related airway dimension, male gender.
- **Nutritional status**: malnutrition is the single most common risk factor of ALRI-related mortality. Low oropharyngeal fibronectin-related poor respiratory mucosao integrity.
- **Immnisation status**: especially with respect to measles, pertussis, diptheria, HiBm etc; most viral URIs don't have preventive vaccines.
- **Socioeconomic factors**: family income, birth order, overcrowding, domestic pollutants from kitchen or parental smoking.
- **Environmental/geographic**: biomas combustion exposure like wood-smoke, day care attendance, school resumption, man-made or natural disasters with consequent squatter/refugee environment. Positive URI symptoms in household contacts, rainy/winter season, Harmattan season.
- **Miscellaneous**: low birthweight, atopy, underlying chronic cardio-pulmonary disease, e.g. bronchopulmonary dysplasia, congenital heart or lung disease, HIV/AIDS, sickle cell anaemia, maternal smoking during pregnancy.

Figure 1 Risk factors of severe ARI and for ALRI

Clinical features

The wide spectrum of clinical manifestations of pneumonia often makes it difficult to distinguish from other ALRI clinical syndromes like tracheobronchitis and bronchiolitis. In general, the clinical presentation of childhood pneumonia varies with the age of the child and the causative agent; the younger the infant, the less specific the clinical presentation.[19,21] The British Thoracic Society guidelines for admission of a child who has pneumonia are given in Figure 3. Young infants below 3 months with pneumonia may present with poor feeding, vomiting, or irritability, minimal systemic disturbance and despite tachypnoea, cough may be absent. On the other hand, systemic disturbance, toxicity, and specific respiratory symptoms and signs are common in infants and pre-school children with a bacterial aetiology. Infants and toddlers with staphylococcal pneumonia are usually toxic and may anaemic at presentation. Furthermore, there may be features of an underlying severe malnutrition, an ongoing or recent measles infection, and/or soft-tissue staphylococcal lesions like impetigo or furunculosis.[19,24,25] Respiratory signs are hardly discriminative of staphylococcal aetiology, but empyema and air-leak respiratory lesions like pneumatoceles, pyopneumothorax are commonly seen.

Most infants and the majority of school-aged children with chlamydial and mycoplasmal aetiology are afebrile with minimal systemic toxicity at presentation. An antedating conjunctival discharge in the first 2 days of life, as well as a stuttering or 'staccato' cough, absence of wheezing, florid radiographic signs, and corroborative haematologic findings like eosinophilia (eosinophils >400 cells/mm^3) are common in young infants with a *Chlamydia trachomatis* aetiology.[19,20] The pre-school, or school-aged child with *S pneumoniae* aetiology is most likely to present with an abrupt onset of systemic and respiratory symptoms, toxicity, respiratory distress including grunting and chest indrawing, as well as signs of lobar consolidation with or without serofibrinous effusion. The pre-school child with pneumonia of Group A β-haemolytic streptococcus (GABHS) aetiology may evolve from a preceding pharyngitic illness, with or without the typical finely papular scarlatiniform rash. An underlying sickle cell disease which predisposes the child to pulmonary infarction, and indeed to a pneumococcal aetiology of pneumonia, is not uncommon in tropical African communities like Nigeria and other sub-Saharan African countries. Mouth flora or an anaerobic bacterial aetiology (e.g. from *Peptococcus*, *Peptostreptococcus*, *Fusobacterium* and *Bacteroides* spp.) is to be anticipated when there are co-morbid states associated with recurrent aspiration (e.g. gastro-oesophageal reflux, craniofacial defects like cleft lip/palate, unconsciousness, neuromuscular/paralytic states like poliomyelitis, and in some tropical communities, infant force feeding).[19,20] Besides *Staph aureus*, aerobic, anaerobic and unusual bacterial agents like *Norcardia*, *Legionella*, *Mycobacterium* and *Actinomycetes* spp. – as well as several fungal pathogens and oropharyngeal commensals like *Pneumocystitis jiroveci*, *candida*, *Aspergillus* – valid considerations must be accorded to unusual fungi/yeasts like *Histoplasma*, *Coccidioides* and *Cryptococcus* in the immunocompromised paediatric host, with an acute or subacute disease course and focal, consolidated or cavitatory lesions.[19,20] Such immunocompromised states include HIV/AIDS, remission state or relapse from malignancies, ongoing/recent cancer chemotherapy, prolonged broad-spectrum antimicrobial or steroid therapy, and, rarely, those awaiting transplantation procedures. For this subset of childhood pneumonias, some viral pathogens like the Cytomegalovirus, Varicella-Zooster, or Herpes simplex are not uncommon.

Viral pneumonias usually have a subacute course, and may begin with coryzal symptom. Concurrent or antecedent respiratory illnesses in other dwellers in the household are common.[19,20] The latter comprise a nasopharyngitis or flu-like illness in adults and older household contacts, as well as a recent diagnosis of croup or bronchiolitis in younger household contacts. Most cases are likely to cluster in the wet seasons (rainy season in the tropics, or winter for RSV lesions), but PIV lesions are also known to peak during the dry-but-cold tropical harmattan, as well as during the fall or spring in a temperate setting.[6,7] Radiographic features include interstitial infiltrative changes radiating from the hilar region and features of hyperinflation. Measles associated pneumonia is rarely of the typical Hecht giant cell interstitial variety. More often than not, measles is complicated by superimposed severe bacterial pneumonia, usually a necrotising agent like *S aureus* or *Klebsiella pneumoniae*.

Bacteria
- *Streptococcus pneumoniae*
- *Haemophilus influenza* (type b non-typable forms)
- *Staphylococcus aureus*
- *Mycobacterium tuberculosis*

Rarely, *Streptococcus pyogenes* and Anaerobic mouth flora, including *peptostreptococcus*

Viruses
- RSV
- Influenza A or B
- Parainfluenza virus (1, 2 and 3)
- Adenovirus
- Measles virus

Mycoplasma
- *Mycoplasma pneumoniae*

Chlamydia
- *Chlamydia trachomatis*
- *Chlamydia pneumonia* (TWAR agent)

Figure 2 Common causes of community-acquired pneumonia in otherwise healthy children

Investigations

Despite the attendant challenges, microbiologic diagnosis remains an invaluable basis for choosing the most appropriate specific treatment, individual case management, and indeed, for determining the most important target pathogens for (locally relevant) vaccine-prevention programme. Yet, the majority of the health facilities in resource-poor countries (including those of sub-Saharan Africa) lack the relevant microbiological facilities. In view of this evident paucity of the relevant microbiologic tools, along with a similar inadequacy of facilities for radiological investigations in the less privileged countries, the most likely aetiology for a particular age-group (and hence the need for antibiotics), is then predicted based

- Oxygen saturation ≤ 92%.
- Respiratory rate >70 breaths per minute in infants or >50 breaths per minute in older children.
- Intermittent apnoea, grunting.
- Difficulty in breathing.
- Infant not feeding or signs of dehydration in older children.
- Family unable to provide appropriate observation or supervision.

Figure 3 British Thoracic Society guidelines: factors indicating need for admission of a child who has pneumonia

on previously documented microbiological data for the locality. However, where the facilities exist, radiological, microbiological and haematological investigations are explored to sort out confusing clinical presentations, identify the extent and severity of the disease, the presence of complications (e.g. pleural effusion, air leak syndromes), exclude other diagnostic considerations (like foreign body aspiration, pulmonary tuberculosis and congenital heart diseases), and frequently, to follow the appropriateness of therapeutic interventions. Also, relatively invasive investigations (including lung biopsies) may be necessary in the immune-compromised subject, in whom the spectrum of potential pathogens is wider, and the presentation frequently atypical.

The essential elements in the investigation of pneumonia are listed below.

Microbiological techniques

The potential therapeutic value of this diagnostic tool is hampered by the difficulty in obtaining appropriate respiratory specimens in children, the majority of whom are unlikely to provide sputum for Gram stain. Lung aspirate specimens (preferrably from a consolidated segment) are the most suitable for identifying the aetiology of bacterial pneumonia, but the procedure may be complicated with haemothorax, pneumothorax, and other air-leak syndromes.[13,26] A definite indication is a poor response to empirically chosen antimicrobials. Blood culture is less invasive, but the expected positive yield is only 10–30%.[15,27,28] It is nevertheless necessary in those with a high fever, toxicity, and high erythrocyte sedimentation rate (ESR). Urine analysis for bacterial antigenuria (of capsulated bacteria like *S pneumoniae* and *H influenzae*) using countercurrent immmunoelectrophoresis, may help identify a bacterial aetiology, even after initiating antimicrobial treatment. Rapid viral diagnostic techniques like immunofluorescence microscopy of nasopharyngeal aspirate or enzyme linked immunosorbent assay (ELISA), and the polymerase chain reaction (PCR) technique are useful for diagnosing pneumonia of viral origin,with or without bronchiolitis.[28,29] However, serological tests remain the valid methods for identifying a chlamydial or mycoplasmal aetiology. Raised serum Cold agglutinins in titres greater than 1 in 128 is highly suggestive of mycoplasma aetiology, while a rise in the antistreptolysin titre will corroborate a group A β-haemolytic streptococcus aetiology.[30]

Radiological

When available, a posteroanterior (PA) chest radiograph (with or without a lateral exposure) is particularly useful in confirming the anatomic diagnosis, identifying the extent of the disease, the presence of intrathoracic complications like pleural effusion and pneumothorax, and excluding differentials like foreign body aspiration. In bacterial pneumonia, a lobar, segmental or bronchopneumonic pattern (with or without effusion) may be evident, while an interstitial pattern with or without hyperinflation is expected in viral or pneumocystis aetiology. Mycoplasma pneumonia is associated with patchy alveolo-interstitial infiltrates in single or contiguous lobes.[19] Some illustrative chest radiographic findings of childhood pneumonia are shown in Figures 4–6.

Other investigative tools

In bacterial pneumonia, a full blood count and differentials, will reveal leucocytosis (>12 000 cells per mm^3 with polymorph predominance), in addition to a raised erythrocyte sedimentation rate (ESR). A mild leucocytosis or leucopaenia with lymphocytosis is expected in viral pneumonia, while *Chlamydia trachomatis* causes pneumonia associated with eosinophilia in early infancy. Serial pulse oxymetry is preferable to the more invasive arterial blood gas monitoring for monitoring oxygen saturation in the hospitalized sick infants and preschool children. The immuno-compromised subject with pneumonia may require an open lung biopsy or bronchoalveolar lavage specimens for histopathology and identification of fungal, bacterial, and non-bacterial pathogens.

Treatment

The management of pneumonia may be divided into two concurrently accomplishable components, namely specific and supportive therapy. In view of the tropical bias of the present discourse, it is deliberately focused on a primary care approach. Newer therapeutic frontiers for viral pneumonias (available in the developed world) are also briefly outlined as appropriate.

Specific therapy

The development of standard protocols for diagnostic discrimination and management of ARI by the World Health Organization (WHO) especially for the first-level/primary care level constitutes the current most effective strategy for stemming the mortality burden of pneumonia in the tropics.[10] This case management approach emphasises capacity building of the lower cadres of the healthcare team for prompt recognition of pneumonia, the initiation of effective antimicrobials, prompt referral of severe cases to higher levels of care, and the provision of follow-up care.

The recommended outpatient antimicrobial for treating children with pneumonia in the third world is cotrimoxazole, chosen because of the ease of administration, efficacy against the common pathogens, and safety profile. Alternative options are amoxicillin, ampicillin, or procaine penicillin. The WHO-recommended specific antimicrobials for severe cases requiring in-patient care are parenteral chloramphenicol and/or crystalline penicillin.[10] It is however important to note that *Staph aureus* and *Klebsiella* species are currently emerging as the top two important pathogens of childhood pneumonia in some urban third world communities in Nigeria, Colombia, and India.[6,7,16,31] Consequently, there may be a need to modify the WHO antimicrobial recommendations to reflect the appropriate ranking of the possible pathogens in such communities. Despite the high cost of β-lactamase-stable

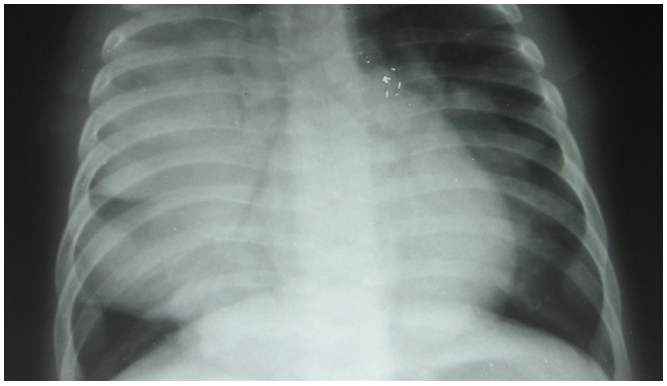

Figure 4 Uniform opacity in the right upper and middle lobes, as well as the near-classic air-bronchogram sign of lobar pneumonia

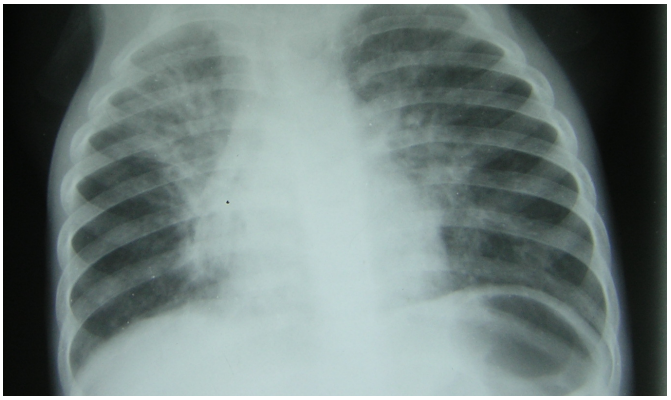

Figure 5 Note interstitial infiltrates radiating from the hilum, suggesting a viral aetiology

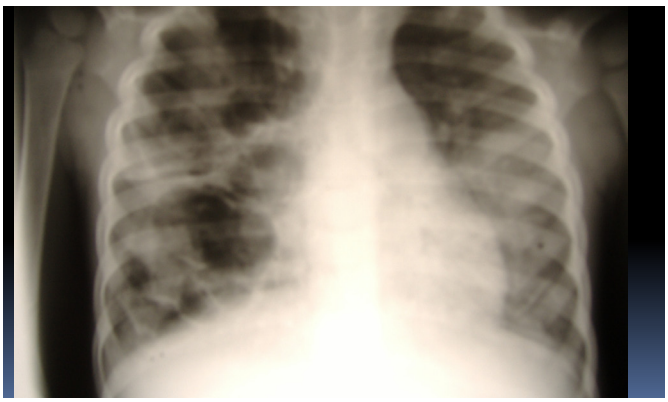

Figure 6 Note multiple patchy infiltrates and pneumatoceles suggestive of a Staphylococcus aureus aetiology

agents like amoxicillin–clavulanate (Augmentin®), or sultamicillin (ampicillin–sulbactam combination), their use is becoming increasingly inevitable for the moderate to severe cases of pneumonia, particularly in the urban tropical paediatric practice. Parenteral aminoglycosides like gentamicin may be combined with any of these semi-synthetic penicillins, not only with synergistic efficacy for Gram-positive pathogens, but for an equally effective coverage of a possible *Klebsiella pneumoniae* aetiology. In the penicillin-allergic patient, parenteral cefuroxime is a suitable substitute. Alternative antimicrobial agents for out-patient cases include oral cephalexin or clindamycin (Dalacin-C®). The antimicrobial spectrum covered by the new-generation macrolides like azithromycin (Zithromax®) is also good enough to earn a recommendation as an alternative oral medication in the ambulatory treatment of moderately severe cases.

Despite an increasing availability of specific antiviral agents which are of potential value for treating viral pneumonias especially in infants with respiratory syncytial virus (RSV disease), the current recommendation is that of 'watchful waiting', while pursuing supportive care (vide infra). However, if the facilities are available, infants with RSV disease with concomitant symptom-complex of bronchiolitis, and in whom there are risk factors of mortality (i.e. preterm delivery, age <2 months, chronic lung disease/broncho-pulmonary dysplasia, and congenital cardiac lesions) may be offered specific antiviral agents like aerosolised ribavirin. For influenza A-associated disease, amatandine (a tricyclic amine) is given. Alternative anti-influenza agents include rimatandine for type A, and neuraminidase inhibitors like oseltamivir or zanamivir for type B.

Supportive care

For ambulatory and hospitalised cases of pneumonia, supportive care constitutes a crucial aspect of the management. The essential elements of the supportive treatment for both categories of patients comprise addressing fever and providing appropriate thermal environment, provision of feeds/food and fluids, as well as clearing the nostrils. Also, the provision of oxygen, as well as instituting appropriate interventions for complications like congestive cardiac failure, severe anaemia, and pleural effusion constitute important elements of the supportive care of the hospitalised child. The indications for oxygen therapy in hospitalised children with pneumonia include severe disease (with the presence of central cyanosis using the colour of the tongue, a child that is too ill to feed or drink, hypoxaemia-related symptoms like restlessness or altered sensorium, severe chest indrawing, severe tachypnoea (with respiratory rate in excess of 70 breaths per minute), and in the case of a young infant less than 2 months, grunting or frequent episodes of apnoea.[32–34]

Other supportive treatment/specific therapy of complications

A trial of a nebulised bronchodilator (salbutamol or ipratropium bromide), preferably driven by compressed oxygen is usually required for those with concomitant bronchiolitic symptoms. Congestive cardiac failure is a frequent complication in infants and toddlers. Such patients will require frusemide. Severe anaemia requires a cautious, frusemide-primed packed cell transfusion.

Finally, for intrapleural complications like pleural effusion including empyema, pneumothorax and air-leak syndromes, prompt surgical drainage/evacuation via a closed under-water sealed tube system is frequently needed. Details of the treatment options for empyema and intrapleural air collection are provided in standard texts.

Prevention and control

The three basic elements of the recommended control strategy comprise:

1. The promotion of the use of standard management plans to identify children with bacterial pneumonia and hence initiate a prompt antimicrobial therapy.
2. Capacity building via training and retraining of different cadres of healthcare workers (from village-level health workers, to community health officers and physicians in primary healthcare and urban referral facilities) to recognise not only the general disease burden of ARI, but the potential mortality risk posed by pneumonia in children.
3. Aggressive pursuit of national programmes on immunisation (NPI) which constitute the cornerstone of accomplishing a meaningful control of some pneumonia-provoking, but vaccine-preventable childhood illnesses like measles, pertussis, and tuberculosis. Also, the control of *H influenzae* ((Hib vaccines) and pneumococcal pneumonia (PCV7, PCV10 and PCV-13)[35,36] and other invasive diseases associated with these pathogens will clearly benefit from the inclusion of their respective vaccines in the NPI.

Other preventive-control strategies

These include the following measures:

- Reducing the current high incidence of malnutrition via a multi-sectoral approach and the provision of micronutrient supplements like Vitamin A and zinc.
- Improving the socioeconomic status and living conditions of families. This includes the provision of adequate ventilation, avoiding overcrowding, and initiating (domestic) behavioural changes to prevent exposure of children to domestic pollutants.
- Pursuit of personal hygiene-related measures like hand washing with soap (especially for viral upper respiratory and pneumonia), covering the mouth while coughing, and avoidance of indiscriminate spitting.

Conclusion

In conclusion, this discourse has attempted to provide valid information about the morbidity and mortality burden of childhood pneumonia in resource-poor countries, the subsisting risk factors of pneumonia-related morbidity and mortality, as well as the consequent need for effective control strategies/measures to stem the current tide. In addition, the discourse has highlighted the major elements of effective treatment, preventive and control measures relating to severe pneumonia/ALRI.

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