Reducing childhood mortality from acute respiratory infections in Malawi

B Larrú

Every year more than 10 million children die worldwide before reaching their fifth birthday. Acute respiratory infections (ARIs) are behind one in five childhood deaths in low- to middle-income countries, and 90% of these deaths are due to pneumonia.[1] More than 60% of childhood mortality in developing countries could be prevented with effective interventions, like those included in the strategy developed by the World Health Organization (WHO) known as Integrated Management of Childhood Illness (IMCI), which contains both preventive and curative elements in family, community, and health facility settings.[2]

WHO has also produced guidelines for the management of common illness wjem resources are limited.[3] Some of these recommendations have already been reviewed and scientific evidence is behind them. However, many of the strategies adopted by WHO to reduce childhood mortality need further review.

The highest rates of child mortality worldwide are reported from sub-Saharan Africa, where around 180 deaths per 1000 live births still occur in some countries.[4] Most of these deaths are due to only five diseases: ARI, diarrhoea, measles, malaria, or malnutrition or a combination of these.[2]

Malawi shares many of the health constraint of sub-Saharan Africa. The country has reported annual prevalence rates of childhood fever, diarrhoea, and pneumonia of 44%, 22%, and 45%, respectively; and mortality rates due to malaria, diarrhoea, or pneumonia represent 14%, 18%, and 23%, respectively, of the total mortality rate among children less than 5 years of age in the country. ARI severely affects morbidity among Malawian children and it is the second leading cause for children attending health facilities.[5] Nevertheless, numerous reports about childhood infections have been published in Malawi during the last 25 years, so a better understanding of childhood ARI can be achieved there, and consequently it is an appropriate country in which to review WHO recommendations.

Beatriz Larrú MD, MSc, PhD
Laboratorio de Imunobiología Molecular
Servicio de Inmunología
Hospital General Universitario Gregorio Marañón
Doctor Esquerdo 46
28007, Madrid, Spain; and
Liverpool School of Tropical Medicine, UK.
Email: bealarru@yahoo.es

Objective

The main purpose of this article about ARI in Malawian children is to look at the evidence behind the WHO Guidelines in this particular setting. The review focuses on pneumonia, due to its high contribution to childhood mortality. More detailed analysis has been done on the management or diagnosis of pneumonia in children. In areas where resources are limited and other infections like HIV or tuberculosis have a high prevalence, knowing whether a child has pneumonia or not, and which is the most effective treatment, are the main two questions that every health professional needs to answer.

Methods

Potential studies for inclusion in this literature review were found through PubMed search using the terms 'pneumonia' (or 'respiratory infection') and 'children' (or 'infant'), and 'Malawi' (or 'Africa'). Only studies written in English, published since 1990, targeting the Malawian paediatric population and focusing on pneumonia were included. Twenty studies meet inclusion criteria and six reviews of the International Child Health Review Collaboration (ICHRC) from WHO's website were also included. Throughout the review, results are given together with authors' opinions and a discussion. Conclusions are expressed after every section and summarised in Table 2.

Literature review

Pneumonias, particularly those with bacterial origin, claim many childhood deaths in developing countries.[6] Thus, the WHO Guidelines recommend that pneumonia should be always considered in children aged 2 months to 5 years with coughing or difficult breathing (or both).[2] Infants under 2 months were not be included in this review because symptoms, aetiology, and management are different from those of older children.[7] Besides, WHO has also produced separate guidelines for ARI among infants <2 months.

Pneumonias are mainly caused by viruses or bacteria. In settings where diagnostic resources are limited, this distinction might be very difficult and it is well known that a dual infection is not uncommon in children (up to 40% in some series).[4,8] For this reason, identifying which might be the more likely aetiology (particularly among bacteria) according to age, season, or underliying pathology can be more relevant in terms of childhood survival.

Nevertheless, several reports from Kenya, Mozambique,

or South Africa have revived interest in the role of viruses such as respiratory syncytial virus (RSV) or human metapneumovirus associated with lower respiratory tract infections, especially among infants with high risk factors like chronic pulmonary diseases or congenital heart diseases.[9–11] Although in WHO's *Pocket Book of Hospital Care for Children* chapters about bronchiolitis or wheeze with cough or cold are already included, little is said about viruses in IMCI Guidelines.[2] Considering that the IMCI strategy has been introduced in many developing countries, publishing the importance of viruses in childhood ARI might help in the future to implement healthcare – including specific treatments for virus like immunoprophylaxis (palivizumab) _ to prevent RSV. However, the desperate situation in many countries in terms of child health makes it more urgent to improve the management of bacterial pneumonia, so as to achieve a higher impact on childhood survival.

As Ayieko and colleagues mention in an ICHRC report,[8] the WHO Guidelines were published 15 years ago, so more up-to-date information about the causes of pneumonia is needed to choose the most appropriate antibiotic for management. Carrying out an aetiological diagnosis is often unfeasible in most countries with limited resources. Besides, an organism identified in the blood of a child with pneumonia can only be considered as the causal agent if pneumonia is associated with bacteraemia.[12] More sensitive techniques such as lung aspiration, serology, or sputum induction are only affordable in research centres. Besides, even in Western settings, all these results will not be ready in time for the initial management of patients, so detailed information regarding the most likely germs behind childhood pneumonia is always needed.[13]

In most sub-Saharan countries, the leading causes of childhood pneumonia are *Streptococcus pneumoniae* and *Haemophilus influenzae* (Hib).[14] Different series identify both pathogens in nearly 50% and 20%, respectively, of all pneumonias with identified aetiological agent (most of the series only isolate an organism in 50% of patients).[8]

More recent data from pneumonia causes in Malawi have been published by Graham and colleagues.[15] After analysing the clinical presentation and outcome of 299 Malawian children with non-typhoidal salmonella (NTS) without evidence of local sepsis over a period of 26 months, they conclude that NTS (*Salmonella typhimurium*) is the commonest isolate on blood culture from children in their centre, particularly during the onset of the rainy season and among children with severe malaria. The relevance of this finding in the aetiology of pneumonia in Malawian children was recently exposed by Mankhambo and colleagues.[16] They reported a lobar pneumonia caused by NTS (*S typhimurium*) in a 16-month-old HIV-uninfected Malawian girl, who, 1 month after an episode of severe malaria (cerebral malaria and anaemia) was admitted to the hospital with a clinical diagnosis of pneumonia, which was afterwards confirmed by blood culture. The relevance that this finding has to selecting the most appropriate treatments will be discussed later.

The introduction in 2001 of the Hib conjugate vaccine in Malawi has dramatically reduced the importance of Hib in the pathogenesis of ARI among Malawian children.[16] In countries like Gambia, before the introduction of Hib conjugate vaccine, around 20% of pneumonias in children between 2 months and 5 years were due to Hib.[8] That has a considerably effect on the empiric treatment for ARI among children and makes the revision of WHO guidelines even more essential. The further introduction of conjugate pneumococcal vaccine in Africa will also have an impact on the aetiology of childhood ARI. Its potential role in reducing antimicrobial resistance among adult pneumococcal isolates would be very helpful especially among HIV-infected adults.[17]

In summary, the most likely causes of pneumonia in Malawian children are *S pneumoniae* and NTS.[16] The association with mortality of high pneumococcal DNA loads in Malawian children with invasive pneumococcal diseases has recently been reported and demonstrates the necessity for the introduction of universal pneumococcal vaccine in this country to reduce childhood mortality.[18] However, the presence of high rates of HIV in Malawi increases the possible aetiologies of pneumonia in children and complicates their diagnoses and further treatment. Thus, a more detailed review will be conducted of lung diseases in children with HIV/AIDS.

More than 90% of children living with HIV/AIDS come from sub-Saharan Africa. In Malawi, a prevalence between 30 and 60% has been reported among children attending large hospitals.[19] The spread of the epidemic has made management of childhood infections more complex, and has sadly demonstrated the weakness of many healthcare systems. Lung diseases are the most common cause of mortality and morbidity among HIV-infected infants according to studies done in Western countries, and sometimes ARI-like pneumonia due to *Pneumocystis jirovecii* (formerly known as *P carinii* or PCP) is the first manifestation of the infection.[14] As Graham et al[19] havehighlighted in their reports, there are many difficulties in confirming a diagnosis of pneumonia among HIV-infected children in resource-poor settings.[19] However, Graham has developed an effective approach to lung diseases among HIV-infected children in Africa.[4] Only the occurrence of pneumonia will be discussed in this review. Nevertheless, the importance of other diseases such as tuberculosis (TB) cannot be forgotten. The HIV pandemic is concurrent with an emergence of TB in all African countries and this is an important cause of lung diseases in African children and adults.[20] The most important causes of lung pathology in HIV-infected children are summarised in Figure 1.

The main cause of pneumonia among Malawian HIV-infected children is bacterial pneumonia due to the same pathogens as in non-infected children.[14] PCP is the most important opportunistic infection in infants, especially

in the first year of life (2–6 months) and is associated with a very poor outcome.[21] As previously mentioned, Graham has developed a practical approach to differentiate bacterial pneumonia from PCP pneumonia among HIV-infected children, based on a report of the clinical presentations of PCP among 16 HIV-infected Malawian children under 6 months of age.[19] PCP was associated with an absence or low-grade fever, severe hypoxia which lasts for more than 48 hours, and clear or diffuse abnormalities in auscultation. Ten of these 16 children died during the 6-month study. Diagnosis of PCP was done with immunofluorescence of nasopharyngeal aspirates and all the confirmed cases and those in which the infection was clinically suspected were given high doses of cotrimoxazole orally with prednisolone when SaO_2 <70%. This report highlights not only the high fatality rate of childhood pneumonia (20.1% of all the pneumonia cases detected during the study died), but also the difficulties for diagnosis of PCP in HIV-children which might explain the lower rates of PCP reported in Africa in the past.[19,22] Almost all the most sensitive techniques, such as broncho-alveolar lavage (BAL), are not available in a resource-poor setting and the lack of intensive care units makes other techniques, such as transbronchial biopsy, highly risky, according to Graham and colleagues.[19]

WHO Guidelines recommend that PCP should be diagnosed in any child with severe or very severe pneumonia and bilateral interstitial infiltrates on chest X-ray, or whose ordinary pneumonia does not respond to treatment.[3] In their ICHRC report, Graham and Wijesingha emphasised that PCP should be suspected and treated in any HIV-positive infants with severe pneumonia due to the high fatality rate.[23] They recommended, when BAL is not available, carrying out the diagnosis of PCP with nasopharyngeal aspiration or induced sputum.[23] According to the series on PCP in HIV-infected children and adults, the inclusion of the last two points will reduce the mortality among Malawian HIV-infected infants.

Graham has also proposed an effective primary prophylaxis against PCP.[24] It includes the administration of co-trimoxazole to all infants born from HIV-infected mothers, from the age of 6 weeks to 6 months. After this age prophylaxis could be continued only among very immunosuppressed children, reducing the chances of developing resistance to other closely related drugs like sulfadoxine-pyrimethamine.[25] The absence of HIV considerations among IMCI Guidelines is now being reconsidered. The inclusion of such effective prophylaxis would have an important impact on the survival of HIV-infected children in Malawi.

Because most health workers in developing countries do not have any diagnostic test when treating children with a cough or difficult breathing, WHO Guidelines establish diagnosis of pneumonia with clinical findings. The WHO *Pocket Book of Hospital Care for Children* states that pneumonia should be considered in every child with: cough with fast breathing, lower chest indrawing, fever, coarse crackles on auscultation, nasal flaring and grunting, or head nosing. Pneumonia is classified as very severe, severe, or non-severe, according to clinical features, with a specific treatment for each category[3] (see Table 1). IMCI Guidelines also promote the same classification for managing children with cough or difficult breathing in primary health centres. All children with very severe or severe criteria for pneumonia should be referred.[2] To improve the treatment of childhood pneumonia it is essential to assess how sensitive and specific these definitions are among Malawian children and, even more importantly, establishing how they could be improved.

Ayieko and English, in their ICHRC report, conclude that hypoxaemia is a common pathway of mortality among infants with pneumonia.[26] Physical signs such as cyanosis, raised respiratory rate, head nodding (due to the use of muscles in breathing), and lethargy or unconsciousness were associated with hypoxaemia. Both authors emphasised that, in spite of not having any reliable single clinical finding with a high specificity and sensitivity to detect hypoxemia in children, the presence of respiratory rates >60 breaths per minute together with an altered mental status had shown to be convenient

Figure 1 Infectious causes of lung diseases among HIV-infected infants according to age (adapted from reference 14)

	Infants	Children
Less common	Measles LIP	PJP Viral pneumonia Measles CMV pneumonitis and other viral pneumonia Malignancy: Kaposi´s sarcoma, lymphoma Fungal pneumonia MAC infection Nocardiosis
More common	Bacterial pneumonia PJP Tuberculosis Viral pneumonia (RSV, influenza) CMV pneumonitis Mixed infection	Bacterial pneumonia Bronchiectasis Tuberculosis Mixed infections LIP

Notes
PJP = *Pneumocystis jirovecii* pneumonia; LIP = lymphoid interstitial pneumonitis;
RSV = respiratory syncytial virus; CMV = cytomegalovirus; MAC = *Mycobacterium Avium* complex

Table 1 Classification of severity of pneumonia and IMCI recommendations (adapted from reference 3)

Clinical finding	Category	Treatment
• Central cyanosis • Severe respiratory distress • Not able to drink • Lethargy or unconsciousness	**Very severe pneumonia**	• Admit to hospital • Give antibiotics and oxygen • Manage the airway • Treat high fever
• Chest indrawing	**Severe pneumonia**	• Admit to hospital • Give antibiotic • Manage the airway • Treat high fever
• Fast breathing: ≥50 breaths/minute in a child aged 2–11 months ≥40 breaths/minute in a child aged 1–5 years • Definite crackles on auscultation	**Pneumonia**	• Home care • Give antibiotics for 5 days • Soothe the throat and relieve cough with a safe remedy • Advise the mother when to return • Follow up in 2 days

in many studies.[26] However, the limitations of measuring respiratory rates, especially among infants, and the non-invasive and accurate properties of pulse oximetry, show that this latter method should be implemented in resource-poor settings like Malawi, where WHO Guidelines focus on the recognition of pneumonia mainly by detecting children with fast breathing.[2,26]

Finally, some aspects of the treatment of childhood pneumonia will be considered. The WHO *Pocket Book of Hospital Care for Children* recommends the following for the treatment of very severe pneumonia:

- ampicillin + gentamicin for 5 days and 5 days more of oral amoxicillin + gentamicin i.m.; or
- choramphenicol i.m. or i.v. until the child has improved and then orally; or
- ceftriaxone.

Failure to respond to this initial treatment indicates the need to consider the addition of antibiotics against *Staphococcus* or enteric Gram-negative bacteria.[3]

These recommendations have recently been supported by Gavranich and Qazi[13] and new findings such as the similar effectiveness of 3 and 5 days amoxicillin treatment for non-severe pneumonia[27] or the promising role of zinc supplementation in the management of ARI have recently been reported.[28] Nevertheless, bearing in mind the epidemiology behind pneumonia in Malawian children, some considerations can be made (see Table 2).

The major role of NTS in childhood bacteraemia, as well as in pneumonia and its frequent pattern of resistance to ampicillin, choramphenicol, and trimetroprim-sulfamethoxazole,[15] explain why gentamicin (plus penicillin or choramphenicol) is recommended as first-line therapy in Malawian children for the treatment of pneumonia or septicaemia.

In a previously reported case of lobar pneumonia due to NTS, gentamicin was not effective due its poor tissue penetration, according to the authors. Consequently third-generation cephalosporin were selected as the most appropriate regimen for severe pneumonia in Malawi by Mankhambo and colleagues.[16] Making these drugs available in every health centre and using them with a rational approach to minimise the chance of resistance, will contribute to reducing mortality among Malawian children.

Future challenges

The inequity of child health worldwide is not only due to the weakness of healthcare systems. Lack of research also contributes to the poor quality of care. For instance, not having an acute knowledge of the aetiological organisms or their resistance patterns makes the choice of the best empirical treatment for pneumonias more difficult and frequently reduces its effectiveness. Therefore, the scientific community has an important role in the era of

Table 2 Priority strategies that should be implemented to reduce mortality among Malawian children with pneumonia

1. The most likely causes of pneumonia in Malawian children are *S pneumoniae* and NTS. Thus, third-generation cephalosporins are the most appropriate regimen for severe pneumonia in Malawian children. Improving their availability will contribute to reducing mortality.
2. Universal vaccination against Hib and Pneumococcus will reduce the number of severe ARIs among children.
3. Pulse oximetry should be implemented in resource-poor settings like Malawi to detect hypoxaemia among infants.
4. Identification of PCP with non-invasive techniques like nasopharyngeal aspiration (NPA), or induced sputum, and early onset of treatment will improve the prognosis of lung diseases among HIV-infected children.
5. Primary prophylaxis against PCP with co-trimoxazole should be used in all infants born from HIV-infected mothers, from age 6 weeks until 6 months. After this age prophylaxis could be continued only among very immunosuppressed children.
6. Scientific reviews of WHO recommendations and a comprehensive adaptation, will improve the health achievements in Malawi.

IMCI. Clinical trials, epidemiological reports, or literature reviews, would help us provide the best quality of care, even with limited resources, and would contribute to giving every child worldwide the right to enjoy the highest standard of health attainable.

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