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Childhood pneumonia in developing countries

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Abstract

Pneumonia is a widespread and common infectious lung disease that causes inflammation, which can lead to reduced oxygenation, shortness of breath, and death. An estimated nearly 1·2 million children younger than 5 years died in 2011 from pneumonia. Most of these deaths occured in developing countries where access to care is limited and interventions that have improved care in developed countries are scarce. Despite substantial increases in our understanding of the clinical syndrome of pneumonia and its aetiologies, its accurate diagnosis is challenging when clinical indicators are relied on, and improves only modestly with addition of laboratory, microbiological, or radiographical tests. Prevention programmes and treatment guidelines have led to impressive reductions in disease, but children remain at risk of misdiagnosis and inadequate treatment. Research to address challenges in the aetiological diagnosis of pneumonia and widespread implementation of treatment interventions beyond vaccines and antibiotics are necessary to mitigate the burden of pneumonia and improve child survival.

Introduction

Pneumonia is a widespread and common infectious lung disease that causes inflammation, which can lead to reduced oxygenation, shortness of breath, and death. Nearly 1·2 million children younger than 5 years die every year from pneumonia.[1] Most of these deaths occur in developing countries where access to care is incomplete and interventions that have improved care in developed countries—including appropriate antimicrobial treatment, routine vaccination, improved nutrition, and effective oxygen therapy—are scarce. In the

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Conflicts of interest

SAQ is staff member of WHO. The expressed views and opinions do not necessarily reflect the policies of WHO. We declare that we have no conflicts of interest.

past 20 years substantial advances have been made in our understanding of the clinical syndrome of pneumonia, its aetiology, and appropriate treatment. We review the treatment of pneumonia in children in developing countries. We focus on the epidemiology of pneumonia morbidity and mortality, examine new areas of understanding in diagnostics and causes of disease, and elaborate on approaches to treatment recommendations and their challenges. Research to address persistent challenges in the aetiological diagnosis and widespread implementation of treatment knowledge are necessary to mitigate the burden of pneumonia and improve child survival.

Pneumonia epidemiology and mortality: estimates and trends

To establish the link between pneumonia and mortality in children worldwide, Williams and colleagues[2] analysed data from 44 countries. They reported estimates of pneumonia-attributable death ranging from 8% to 36% and showed a log-linear association that, when indexed to the global population in the year 2000, produced a worldwide mortality estimate in children younger than 5 years of 1·9 million (range 1·6–2·2 million) deaths due to pneumonia. More recent studies based on improved data have further ratified this estimate and have additionally shown a decrease in pneumonia-attributable deaths since Williams and colleagues' publication (figure 1).[7–10] Deaths caused by pneumonia have decreased by an average of 3·1% per year to 1·4 million in 2010,[7] or to as low as 847 000 according to a report of the Global Burden of Disease (GBD) Study.[11] However, the data from the GBD study are derived from models integrating a large number of observational studies with highly variable outcomes, and might therefore be less accurate. A more reliable estimate for mortality in children younger than 5 years attributable to pneumonia is 1·2 million in 2011, as reported by the Child Health Epidemiology Reference Group.[12] Although this estimate represents 18% of total child deaths in 2011, it is based only on data that classed pneumonia as the main cause of death rather than as an associated cause of death. Therefore, the estimates of pneumonia-related mortality could be much higher. Additionally, these figures account for deaths in HIV-negative populations and are therefore probably underestimates, especially in view of the high prevalence of pneumonia deaths in settings with high HIV burden.

The proportion of childhood deaths due to pneumonia has not remained constant. Results of global estimate studies have shown that pneumonia deaths, as would be expected, fall as child mortality decreases not only in actual number, but also proportion of total deaths.[2,7] Data collected from 2000 to 2008 in China corroborate this finding,[13] and show that as child mortality fell by nearly 47% from 39·7 to 18·5 deaths per 1000 livebirths, the proportion of deaths attributable to pneumonia decreased by nearly 40% from 28% to 17% of total deaths. The best-fit projections applied by Williams and colleagues[2] clarify this point by projecting a decrease in the estimated proportion of pneumonia deaths from 23% to 11% of total deaths as mortality rates fall from 50 to 5 per 1000. Since pneumonia as an associated cause of death is not taken into account in these analyses, interventions directed at pneumonia could have a greater total effect on mortality by improving outcomes from other diseases, including HIV or measles. General improvements in health could also have a greater than expected effect on pneumonia transmission or illness severity and ultimately death.

Part of this decrease in pneumonia deaths over the past decade is directly attributable to prevention programmes and the use of pneumococcal and *Haemophilus influenzae* type B (Hib) vaccines, which reach 31% and 60% of the world's children, respectively.[14,15] Despite these efforts, incidence and mortality attributable to pneumonia, including neonatal pneumonia with its unique diagnostic and treatment challenges, remain high in many areas. Rudan and colleagues,[10] investigating data from rural areas and developing countries, calculated a median incidence estimate of roughly 280 episodes of pneumonia per 1000 children younger than 5 years per year. This high incidence in children makes clear that pneumonia control through effective prevention programmes based on vaccination would be a suboptimum singular approach and that an additional emphasis on improvement of treatment is essential

Causes and diagnosis

Causes of pneumonia

Appropriate and targeted treatment of an illness needs correct diagnosis. Unfortunately diagnosis of pneumonia is particularly difficult because most approaches and guidelines that direct empirical treatment are based on studies of bacterial pneumonia from the 1980s. These studies highlighted two pathogens—*Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* type B (Hib)—as the main causes of severe childhood pneumonia.[16] Global modelling techniques have led to the estimation that, in 2000, there were 13·8 million cases of pneumococcal pneumonia and 7·9 million cases of Hib pneumonia resulting in 41% and 16% of total pneumonia deaths in children, respectively.[17,18] In view of the relatively high effectiveness of commonly used β-lactam therapy for severe pneumonia, the true proportion of pneumococcal disease is probably even higher than suggested by these estimates and many cases of pneumococcal pneumonia probably remain undiagnosed. A marked difference can be seen when observed mortality attributable to pneumococcal pneumonia derived from vaccine studies is compared with that presented as part of global estimate studies (figure 2). Viral causes, although less thoroughly studied, probably account for a substantial proportion of severe presentations of pneumonia.

Several developments have advanced understanding of the causes of pneumonia since the 1980s studies. The first such development is the incidence and spread of HIV infection, which has occurred in areas with disproportionately high numbers of pneumonia deaths such as parts of sub-Saharan Africa and Asia. Several studies have shown that the high mortality in this HIV population is often driven by respiratory illness and that the causes of infection in these cases are more likely to be varied and include pathogens unique to immunocompromised hosts—eg, those with TB or PCP.[20] The variable rollout of antiretroviral therapy throughout sub-Saharan Africa and Asia continues to modify this interaction between HIV and pneumonia. The second development has been the improvement of vaccination programmes worldwide, focusing predominantly on pneumococcus and Hib but also making steady gains in coverage for pertussis and seasonal influenza.[21] Finally, over the past 30 years, unprecedented changes have occurred in general and social determinants of health. The combined forces of urbanisation, increased education, changes in nutrition, improved indoor air quality, reduction of parental tobacco

smoking, and improvements in health-care access will probably have a substantial effect on pneumonia transmission and illness trajectory.

These trends mean that present approaches to pneumonia diagnosis and treatment are outdated and draw attention to the need for new data, especially with the use of advanced diagnostic technologies that can better identify known causes, and causes that have remained elusive despite exhaustive testing. The large, multicountry Pneumonia Etiology Research for Child Health (PERCH) project that is underway in several countries will address some of these issues and provide a clearer understanding of viral and bacterial causes of pneumonia.[22]

Diagnostic challenges

Pneumonia is a pathological diagnosis, but treatment decisions often rely on use of surrogate clinical or microbiological data. However, clinical data are often imprecise, and microbiological data can be challenging to interpret. Additionally, chest radiographs, often used as the gold standard in pneumonia diagnosis studies, are limited by their lag behind clinical presentation and inability to differentiate the aetiology of the disease—ie, bacterial from viral. In a tertiary care emergency department facility in the USA, Neuman and colleagues[23] showed that no particular clinical finding had significant sensitivity in prediction of radiographic pneumonia. Even when simultaneously taking into account several clinical factors—including hypoxia, history of fever, focal decreased breath sounds, and the absence of wheezing—the investigators were unable to separate patients younger than 5 years into distinct likelihood categories for definite radiographic pneumonia. To guide first-level (based in community clinics) health-care workers in management of pneumonia in developing countries, WHO recommends a diagnostic algorithm that takes into account clinical signs that are relatively easy to assess, including age-specific respiratory rates, lower chest indrawing, and several key danger signs such as cyanosis and the inability to feed. When this algorithm has been compared with chest radio graphs, both sensitivity and specificity for diagnosis of pneumonia have been low.[24] The addition of fever and hypoxia to the WHO algorithm has not significantly improved the specificity for diagnosis of radiographic pneumonia. Findings from several studies further elucidate the challenge of pneumonia diagnosis, showing that 5–10% of patients presenting with fever and leucocytosis had radiographic pneumonia even in the absence of respiratory distress or auscultatory findings.[25,26]

These findings raise the question of whether chest radiography is an optimum gold standard for pneumonia diagnosis. Studies assessing the WHO defined algorithm for interpretation of chest radiographs (mostly for use as end-points in vaccine studies) have shown mixed results.[27] Results of a study in Israel examining interpretations based on WHO criteria on 200 chest radiographs concluded that, although agreement was high for cases of alveolar pneumonia and no pneumonia, there was significant disagreement and overdiagnosis by the WHO criteria in the setting of non-alveolar pneumonia.[28] Results of another study in several Argentinian paediatric emergency departments showed that WHO radiograph criteria underestimated the presence of any infiltrate when compared with assessments by paediatric pulmonary radiologists.[29] Part of the difficulty with interpretation of chest radiographs

is the wide array of inflammatory responses triggered by various causes of pneumonia. Although alveolar or lobar infiltrates were previously thought to be pathognomonic for bacterial pneumonia, evidence shows that viral infection and viral and bacterial co-infection can cause similar radiographical findings, and that the possible radiographical difference between bacterial and viral causes of pneumonia does not exist in cases of mild or moderate disease.[30]

On the basis of the low specificity and sensitivity of clinical data in diagnosis of pneumonia, microbiological confirmation as a gold standard of diagnosis seems rational. However, this approach also has challenges depending on the site of specimen collection and specific pathogen identified. Despite its importance as the most frequent cause of bacterial pneumonia, pneumococcus is often found in a carrier state in the nasopharynx of healthy community controls or hospitalised patients who do not have pneumonia.[31] Evidence shows that this carrier state might also occur in the case of viral pathogens that were previously thought to be present only in specimens from patients with true pneumonia.[30] Lung aspirate specimens, bronchoalveolar lavage, or thoracopic biopsy would probably have the greatest correlation with the true pathological diagnosis of pneumonia, but they necessitate invasive procedures that are not commonly used. Taken together, these analyses of clinical and microbiological correlates of pneumonia emphasise the need for improved diagnostic methods that can ascertain true pneumonia and guide treatment, although empirical approaches will probably remain the basis of pneumonia treatment for the foreseeable future.

Novel diagnostics

The search for new diagnostic methods not only concerns the accurate identification of pneumonia but also the identification of disease in which antibiotic use is appropriate. In view of the widespread practice of empirical treatment in outpatient and low-income settings, diagnostics should also be low cost and easy to operate. Because of the emphasis on bacterial causes of severe disease, blood culture gained early ground as an adjunct to pneumonia diagnosis. The advantage of blood culture is that it not only provides a cause but also enables antibiotic resistance testing and, in the case of pneumococcus and Hib, for serotyping, which is crucial for vaccination programmes.[32] The disadvantages of blood culture are that results are available only 24–48 h after presentation, and that its already low yield is further diminished by pretreatment with antibiotics—a common practice before health facility referral in many developing countries.

Use of molecular techniques has shown some potential benefit to address these shortcomings, as shown by Resti and colleagues,[33] who recorded increased sensitivity of identification of bacteraemic pneumonia when comparing blood PCR assays with blood culture. However, consistent with previous studies, the investigators noted that both techniques functioned best in children with severe disease, often with associated complications such as pleural effusion or empyema, and had very low yields in mild or moderate cases.[34] These findings indicate that childhood bacterial pneumonia is unlikely to be bacteraemic in most cases and rarely results from haematogenous seeding of the pathogen to the lungs. In turn, these notions suggest that to improve diagnosis across all disease

severities, diagnostic tests using blood specimens should focus on markers of bacterial infection or specific host immune response rather than the search for a particular organism.

An attempt to apply such a concept by testing urine for serotype-specific pneumococcal antigens has shown promise in adults, producing positive results in 70–87% of those with pneumonia.[34] Quantitative approaches such as the Luminex assay, which needs low sample volume and can test for multiple serotypes simultaneously, have shown even better performance in adults, with a reported sensitivity of 97%.[35] In children, however, the immunochromatographical method has failed because of the inability of current tests to differentiate chronic and asymptomatic carrier states from active pneumococcal infection; more specific and refined platforms could be evaluated.[36] Alternative ways to assess the likelihood of bacterial pneumonia by focusing on inflammatory markers produced by the immune system have identified two candidates with potential benefit: C-reactive protein and procalcitonin. Initially, these biomarkers seemed to to discriminate only between illness severity rather than presence, making them less clinically useful and better suited to enriching a study population for bacterial pneumonia in vaccine trials.[37] More recent studies, however, have shown that although a rise in C-reactive protein concentration is non-specific, the use of procalcitonin as part of a hospital-based treatment algorithm could be meaningful in some settings.[38]

As a result of the limitations of blood specimens for direct identification of pathogens, some investigators have applied molecular techniques to sputum or nasopharyngeal specimens.[31,37] Testing of these specimens has been hampered by the challenge of finding molecular targets that are unique to bacteria causing infection. Some of the tested probe targets, including the *ply* gene that encodes pneumolysin in pneumococcus, are also shared by non-pathogenic oral streptococcal flora, leading to false-positive tests and thus poor specificity.[37] More specific pneumococcal targets such as a region of *lytA* have shown greater promise in differentiation of disease from carrier state, particularly when identified in high density on quantitative PCR.[37] However, definition of a disease-discerning threshold for quantitative results in children remains a challenge because of the high pneumococcal density in carriers.[39,40]

In addition to allowing specific identification of bacterial pathogens, advances in molecular techniques such as PCR have clarified the role of viruses in childhood pneumonia.[41–45] These techniques have shown that viral pathogens can cause a significant pneumonia disease burden beyond the expected contribution from bronchiolitis or reactive airway disease, often resulting in co-infection with other viruses or bacteria. The most commonly identified viruses include respiratory syncytial virus, influenza virus, adenovirus, parainfluenza virus, and human metapneumovirus. In addition to finding these known pathogens, PCR techniques have allowed identification of high levels of other viruses such as rhinovirus, bocavirus, and the newly discovered HKU1 virus.[45] The role of HKU1 virus in causing disease in the lungs is unclear, especially because this virus also occurs frequently in the nasopharynx of healthy children.[41] Advances in multiplex assay and other molecular technologies that can rapidly identify the presence or absence of many key organisms simultaneously nonetheless have great promise for improvement of pneumonia diagnosis.

Treatment

Initial approaches

WHO made the first general recommendations for treatment of pneumonia in 1981.[46] The recommendations were written in response to the high projected mortality from pneumonia, caused by pneumococcus and Hib in particular. WHO's approach emphasised training of first-level and community-level health workers to recognise simple symptoms of disease and make decisions about appropriate treatment and referral. Specific treatment recommendations prioritised use of widely available β-lactam antibiotics but also introduced a potential role for co-trimoxazole, which was relatively new at the time.[47] This empirical approach attempted to balance appropriate therapy with the resource-poor environment of community health-care settings in developing countries. In 1992, after substantial experience with the implementation of this systematic approach, WHO compiled its recommendations for acute respiratory infection case management of disease into the Integrated Management of Childhood Illness (IMCI) guidelines.[48] Early versions of these guidelines established a distinction between non-severe pneumonia (fast breathing), severe pneumonia (lower chest indrawing), and very severe pneumonia (danger signs), and suggested co-trimoxazole as the first-line agent for treatment of non-severe pneumonia. When appropriately implemented, these guidelines have resulted in substantial reductions in child mortality of up to 20%.[49] WHO has continually refined the IMCI guidelines in response to evidence arising from their implementation, with major technical updates published in 2005 and 2012.[50,51] Many studies of the comparative effectiveness of antibiotic regimens done in monitored settings—eg, in hospital—have played an important part in strengthening of evidence behind treatment recommendations in these updates.[52,53]

Despite their establishment as the standard of care in many settings, the WHO guidelines are not always reliably implemented.[49,54] Substantial variability in provider training, medication availability, and diagnostic abilities could underlie the inconsistent application of these guidelines. In some instances, such divergence could be appropriate and a result of additional information such as antibiotic susceptibility testing or rapid malaria testing. More commonly, however, divergence from the intended use of the IMCI can lead to inappropriate treatment and misuse of antibiotics.

Treatment recommendations

The technical update of the WHO recommendations for management of pneumonia, released in early 2013, presents several key changes, including a reclassification of pneumonia categories.[55] Previous categories of non-severe pneumonia and severe pneumonia have been combined to form, respectively, the fast breathing and chest indrawing components of a revised pneumonia category. The previous category of very severe pneumonia has been removed, and children with cough or difficulty breathing in the setting of danger signs are included in the revised severe pneumonia category. Specific treatment changes include recommendation of amoxicillin (rather than co-trimoxazole) as first-line treatment for fast breathing pneumonia, no recommendation of antibiotic treatment for children with fast breathing pneumonia with wheezing but without fever, and

recommendation of oral amoxicillin rather than injectable therapy for treatment of lower chest indrawing pneumonia (panel).

The replacement of co-trimoxazole with amoxicillin as the preferred agent for oral treatment of non-severe pneumonia has been gradual. Initial studies comparing the two drugs were limited by small sample sizes and inconsistent definitions of treatment failure.[47] Subsequent larger studies showed high failure rates in some groups given co-trimoxazole, with increasing resistance often proposed as an explanation.[56] The clinical relevance of resistance patterns, however, has not been adequately investigated for pneumonia, and as such is largely derived from studies of acute otitis media—another common childhood disease that implicates many of the same bacterial organisms.[57] These studies have shown that in-vitro co-trimoxazole resistance correlates with poor clinical outcome and treatment failure;[47] however, application of these data directly to the context of pneumonia is problematic because of clear pharmacological evidence showing that co-trimoxazole reaches lower concentrations in the middle ear compared with lung tissue, suggesting that higher drug concentration in the lung might allow greater activity in pneumonia. Despite this caveat, evidence supports increasing co-trimoxazole resistance in pneumococcal isolates from children with pneumonia. In one such study, investigators examined pneumococcal isolates from children with pneumonia in South Africa between 2003 and 2008, and showed 55% overall non-susceptibility to co-trimoxazole.[58] This result suggests that despite the low cost, wide availability in resource-limited settings, and persistent benefit as prophylaxis, the use of co-trimoxazole in pneumonia is no longer likely to be an effective strategy.

The recommendation to no longer treat fast breathing pneumonia when it occurs with wheezing in afebrile children has also been a gradual process, with the intention to limit antibiotic overuse. This change in recommendations is based on an increased understanding of the suboptimum performance of the WHO diagnosis algorithm in children with wheeze and an acknowledgment that the presence of fever is suggestive of a bacterial cause in the wheezing population.[51] Additionally, results of two studies from Pakistan have shown that in children with non-severe pneumonia the risks of treatment failure or disease relapse are generally low and not significantly different in studies comparing amoxicillin with placebo.[59,60]

The recommended change from intravenous to oral antibiotics for treatment of chest indrawing pneumonia is similarly based on comparative efficacy data. Results of a series of studies undertaken between 1988 and 2010 in settings ranging from low-resource community hospitals to tertiary paediatric centres have clearly shown the equivalence of oral amoxicillin in low-HIV-burden populations when compared with injectable regimens of similar antibiotics.[51,61] The results show no significant difference in treatment failure, disease relapse, or death between injectable and oral antibiotic treatment groups. Overall, these changes in recommendations empower first-level health-care providers to use antibiotics more appropriately and provide home-based care for children who they previously would have referred, leading to increased therapy compliance with risk of few adverse events.

Treatment challenges

Despite extensive research into the effectiveness of treatment approaches and insight into novel diagnostic tests, some challenges to the treatment of pneumonia remain. These challenges can be grouped into two general themes: ensuring sustained benefit from treatment of pneumococcus, particularly in the setting of serotype shifts and antibiotic resistance, and improvement of treatment in specific populations such as patients with HIV co-infection or those affected by pathogens other than pneumococcus. Additionally, there are important systemic challenges to treatment including variable access to care because of geographical or financial obstacles, inappropriate care seeking, and scarcity of antibiotic formulations suitable for children, such as amoxicillin suspension.[62–64]

A large part of the approach to control of pneumococcal pneumonia has depended on vaccination programmes. However, more than 90 individual serotypes of the bacteria exist, and effective immunisation against pneumococcus necessitates neutralisation of the specific capsular polysaccharides that stimulate the immune system and cause lung inflammation. Available vaccines have progressively incorporated more serotypes, focusing on those associated with the greatest disease burden, and whole-cell techniques could provide greater immunogenicity. The way in which serotypes change in response to vaccine programmes further complicates vaccine implementation. For example, use of p*neumococcal conjugate vaccine* (PCV) 7 in the USA led to a decrease in invasive pneumococcal disease, but has also resulted in a concomitant increase in complicated pneumonia (associated with empyema or pleural effusion) of up to 50%.[65,66] Yu and colleagues[67] attributed this finding to an increasing prevalence of non-PCV7 serotypes, such as 19A. Results from other regions, however, emphasise the complexity of making conclusions about the association between serotype shifts and the selective pressure exerted by vaccines. In an analysis from Bangladesh comparing serotypes between 1992–95 and 2004–07, Saha and colleagues[68] showed serotype shifts of similar magnitude in the absence of vaccine implementation in the intervening period, suggesting that time alone can lead to significant shifts in pneumococcal serotypes. More importantly, studies in Finland, USA, and The Gambia have shown greater effectiveness of pneumococcal vaccines than would have been expected based on targeted serotypes.[19,69,70] In either case, even after the rollout of PCV13, pneumococcus will probably continue to account for a large proportion of the pneumonia mortality burden. Figure 3 presents a best-case PCV13 implementation scenario, showing the persistence of pneumococcal pneumonia (non-vaccine type) despite successful vaccine implementation.

Serotype shifts have implications for treatment not only by affecting disease severity but also potentially affecting antibiotic resistance. Crowther-Gibson and colleagues,[58] in an examination of pneumococcal isolates from South Africa, showed an increase in penicillin and multi-drug resistance that resulted from the increased spread of a few key serotypes (6B, 9A, 14, and 19A) that are predominant in paediatric populations and have a propensity for development of resistance. Between 2003 and 2008, these investigators showed an increase in resistance based on meningeal breakpoints (thresholds for assigning resistance to an organism) with penicillin non-susceptibility rising from 23% to 38% ($p<0{\cdot}001$).[58] Penicillin resistance correlates well with multi-drug resistance, and similar increases in multidrug resistant pneumococcal isolates have occurred over the same period.[71,72] In addition to the

possibility of vaccine-induced shifts to more resistant serotypes, high rates of co-trimoxazole use coupled with persistent nasopharyngeal colonisation in children have probably allowed for the selective pressure leading to the emergence of resistance. This interaction has a variable effect on bacterial fitness for survival, with newly resistant strains becoming more virulent in some cases and less so in others.[73,74] Generally, these findings show the need to continue to carefully assess the pneumococcal genomic response to PCV rollout, including monitoring of serotype shifts and antibiotic resistance and identification of proteins that could be targets of future vaccination strategies. Models analysing the spread of antibiotic resistance have shown that reduced antibiotic use leads to decreased resistance, making the case not only for PCV vaccination to reduce antibiotic use, but also for a focus on improved diagnosis of bacterial pneumonia and antibiotic stewardship.[75,76]

The non-pneumococcal category of pneumonia also needs increased focus. Seasonal influenza, for example, can cause primary viral pneumonia and synergistically leads to poorer outcomes in the presence of pneumococcal infection.[77] The increased global experience with seasonal influenza and the increase in use of anti-viral drugs have made implementation of widespread seasonal vaccination and empirical antiviral treatment more plausible than it has been previously. These approaches, or others specifically targeting viral causes of pneumonia, have not yet been widely implemented within community-based health programmes in developing countries, but their potential benefit was shown by a prenatal maternal immunisation project in Bangladesh[78] and is being assessed in two clinical trials (NCT01248715 and NCT01319955). Another underused area to consider for improvement of pneumonia morbidity relates to infections caused by *Bordetella, Mycoplasma*, and *Chlamydophila* species, which have inherently poor response to the β-lactam antibiotics and are difficult to diagnose through routine microbiology.[79] Further investigation of the true burden of disease attributable to these bacteria with molecular techniques is necessary to improve understanding of the potential benefits or absence thereof of empirical treatment with macrolide antibiotics.

Other special populations that could benefit from alternative approaches to management include those with HIV or malaria co-infection. The WHO recommendations for treatment of pneumonia vary slightly by HIV prevalence.[51] For example, duration of treatment with amoxicillin in the setting of non-severe pneumonia without wheeze is 5 days rather than 3 days in areas with high HIV prevalence. This difference is attributed to the fact that studies showing similar benefits with short-course therapy have been done predominantly in regions of low HIV prevalence, thus precluding the generalisability of the findings to high-HIV-burden areas.[61] More important than variations of treatment duration, however, are the questions about situations unique to the immune-compromised state, including increased frequency of otherwise uncommon causes of pneumonia such as pneumocystis and tuberculosis or increased severity of disease with common pathogens. An additional complexity to treatment of pneumonia in children with HIV is the significantly increased risk of infection with multidrug resistant organisms.[58] Both in the case of relatively simple treatment regimens for pneumococcus and complex ones for tuberculosis, treatment guidelines targeting children with HIV need to be adaptable and provide several different regimens to overcome the probable poor response to first-line antibiotics.

Malaria-endemic areas also present unique challenges to the appropriate treatment of pneumonia. These challenges mainly arise from the diagnostic complexity that occurs because of the overlap in symptoms of the two diseases.[80,81] Children with malaria can present with difficulty in breathing associated with anaemia or fast breathing associated with fever. The high prevalence of fever in the setting of malaria might be part of the reason why the addition of fever to pneumonia diagnosis algorithms does not consistently improve sensitivity.[80] Additionally, as in the case of HIV, questions remain about whether causes of pneumonia differ in areas of high malaria burden or whether different approaches to treatment, including combination treatments, are more likely to be beneficial in the setting of co-infection.

Beyond antibiotics

Antibiotics alone are inadequate as a strategy for the treatment of pneumonia because of pneumococcal serotype shifts and increasingly drug-resistant pathogens. Reed and colleagues[82] developed an illness severity score in South African children hospitalised with pneumonia and showed that hypoxia and malnutrition were the strongest predictors for mortality in children without HIV (odds ratio 15·2, 95% CI 5·9–39·4 and 14·5, 6·6–31·6, respectively). Both factors were also the strongest mortality predictors in children with HIV. These findings draw attention to the importance of providing appropriate oxygen therapy, which includes frequent monitoring of oxygen saturation, to reduce pneumonia-related mortality and morbidity. Fulfilment of such an aim is increasingly plausible as devices to measure oxygen saturation become low cost, mobile, and widespread throughout developing countries.

In its 2013 technical update of the IMCI guidelines, WHO affirms the importance of oxygen therapy by establishing oxygen delivery and monitoring systems as a universal standard of care, and recommending that a concerted effort be made to increase their availability worldwide.[51] In making these recommendations, WHO draws on several studies showing that pulse oximetry is accurate at identification of hypoxia and that its use necessitates less training compared with reliance on clinical signs. Furthermore, available pulse oximetry systems are fast, non-invasive, and need no additional infrastructure. Results of studies from The Gambia, Malawi, and Papua New Guinea have also shown that oxygen concentrators that can distil oxygen from room air are effective and low cost.[82–84] Data accumulated so far have informed the WHO recommendation of therapy cutoffs of 90% oxygen saturation for people living at lower than 2500 metres above sea level and 87% for those living above 2500m. Evaluations of oxygen therapy before and after intervention with these criteria have shown 35–50% reductions in pneumonia mortality.[85] Additional evidence of the implementation of low-cost oxygen technology extending to continuous positive airway pressure machines for treatment of severe disease will be important to ensure that appropriate supportive care is provided to children with pneumonia.

A focus on ways to improve management of pneumonia in addition to antibiotics has increased emphasis on programmes that provide a package of care aimed at child survival programmes and improvement of pneumonia outcomes (figure 4). Nutritional inter ventions that can not only prevent malnutrition but, as in the case of zinc, also reduce pneumonia

mortality,[86] are key to such packages. The Lady Health Worker programme in Pakistan has successfully implemented community-based strategies.[87] This programme provides a range of health promotion and basic treatment services in areas with few physicians, and has shown successful home treatment of chest indrawing pneumonia.[52,53] Such programmes can provide integrated services aimed at increasing immunisation rates, promoting adequate nutrition, and ensuring therapy compliance. These interventions are all crucial to a comprehensive plan for the reduction of morbidity and mortality associated with pneumonia, and have been compiled into a framework developed by WHO and UNICEF known as the Global Action Plan for Prevention and Control of Pneumonia (GAPP).[88] GAPP has three broad areas, each with additional recommendations for community-level programming: provision of good nutrition and a healthy environment, prevention of childhood pneumonia, and treatment of children with pneumonia. The first emphasises the importance of breastfeeding and reduced exposure to air pollution, and the others build on vaccination against pneumococcus, Hib, and influenza, and teach recognition and appropriate treatment and referral of disease.

To succeed, community programmes such as these need strong political and financial support in addition to reliable immunisation, testing, and treatment resources. Cohen and colleagues[14] draw attention to the challenges that exist in implementation of such a framework, including the local human resource challenges to ensure that an appropriate number of community workers are available to meet the high demands of interventions such as malnutrition treatment programmes and therapy observation. Challenges also include more systemic barriers such as policy frameworks that appropriately empower community health workers to treat pneumonia with antibiotics and establish consistent funding to support the infrastructure needed for successful management of programme components such as vaccination.

Conclusion

Pneumonia is a common and complex infectious disease, with causes that are rapidly changing worldwide. Its diagnosis is challenging when clinical indicators are relied upon, and improves only slightly with the addition of laboratory, microbiological, or radiographical tests. High exposure of children to respiratory pathogens and overlapping common disease endpoints in children put them at increased risk of being misdiagnosed or inappropriately treated. Attempts to show distinct clinical syndromes based on cause to improve diagnosis and treatment have not succeeded, even with use of innovative PCR-based techniques for the identification of pathogens. Vaccines and effective antibiotic treatment have led to impressive reductions in disease but are at risk of diminishing returns if used inappropriately or if resulting in unanticipated shifts in pathogen types or antibiotic resistance. Despite these challenges, our understanding of pneumonia is increasing, particularly its cause and appropriate treatment. A concerted effort to further understand the disease while providing a package of prevention and treatment interventions beyond vaccines and antibiotics is crucial to improve child morbidity and mortality. In view of the interplay between pneumonia and other childhood diseases, such an effort will probably produce beneficial effects beyond the scope of pneumonia and lead to substantial improvement in child health in general.

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Key messages

- The global burden of childhood pneumonia is high despite advances in our understanding of the clinical syndrome and the introduction of vaccines targeting *Haemophilus influenzae* type b and *Streptococcus pneumoniae*. An estimated 1·2 million children aged less than 5 years died of the disease in 2011.
- Clinical, laboratory, or radiographical diagnostics often cannot show a clear cause of disease, although *Streptococcus pneumoniae* is likely to have a larger role than that currently estimated, and a substantial number of cases are probably due to simultaneous infection with many bacterial or viral organisms.
- Further development of microbiological techniques such as multiplex PCR and organism-specific assays will help to identify the causes of childhood pneumonia.
- Improvement in care of childhood pneumonia will also depend on clear treatment guidelines, improved antibiotic stewardship, and increased availability of appropriate treatments, including child-friendly antibiotic formulations.
- Broadening of community-based prevention and treatment programmes and support of health facilities to provide treatments beyond antibiotics—including improvement of supportive care and availability of supplemental oxygen—are crucial to decrease the burden on childhood pneumonia.

Panel: Highlights of the 2012 technical update of the WHO recommendations for integrated management of childhood illness for pneumonia

Pneumonia

Fast Breathing

- Without wheeze:
  - If in low HIV prevalence area, oral amoxicillin for 3 days
  - If in high HIV prevalence area, oral amoxicillin for 5 days
  - If treatment fails in either setting, refer to health facility
- With wheeze:
  - As without wheeze, if fast breathing persists after bronchodilator challenge

Chest Indrawing

- Treat with oral amoxicillin for 5 days
- If HIV co-infection, treat as per HIV guidelines
- Oxygen therapy as needed

Severe Pneumonia

- Treat with parenteral ampicillin (or penicillin) and gentamicin
- If treatment fails, give ceftriaxone
- Oxygen therapy as needed

Search strategy and selection criteria

References for this Review were identified through searches of PubMed for articles published from January, 2010, to November, 2012, with the terms “pneumonia”, “community-acquired pneumonia”, “acute respiratory illness”, “lower respiratory tract infection”, “pediatric”, “paediatric”, and “childhood”. A specific discussion of neonatal pneumonia was beyond the scope of this Review. Articles identified from these searches and relevant references cited in those articles, including those from before 2010, were reviewed. We included articles in Chinese, French, and German with English abstracts, and all articles with full text available in English.

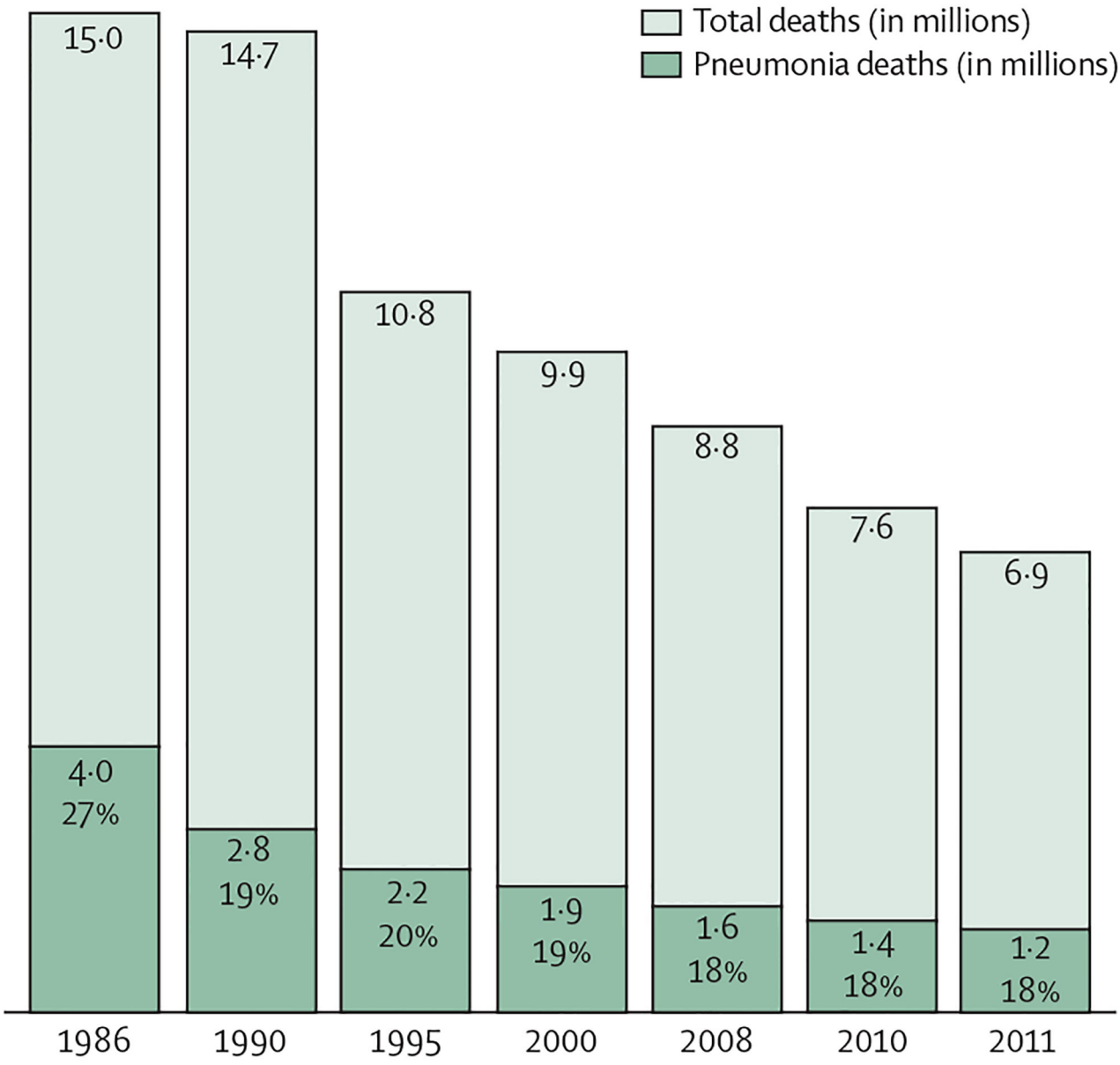

Figure 1: Global estimates of mortality in children younger than 5 years

Proportion of deaths attributable to pneumonia is represented in millions by year. Years for which data have been previously published are shown. Sources: 1986,[3] 1990,[4] 1995,[5] 2000,[2] 2008,[6] 2010,[7] 2011.[4]

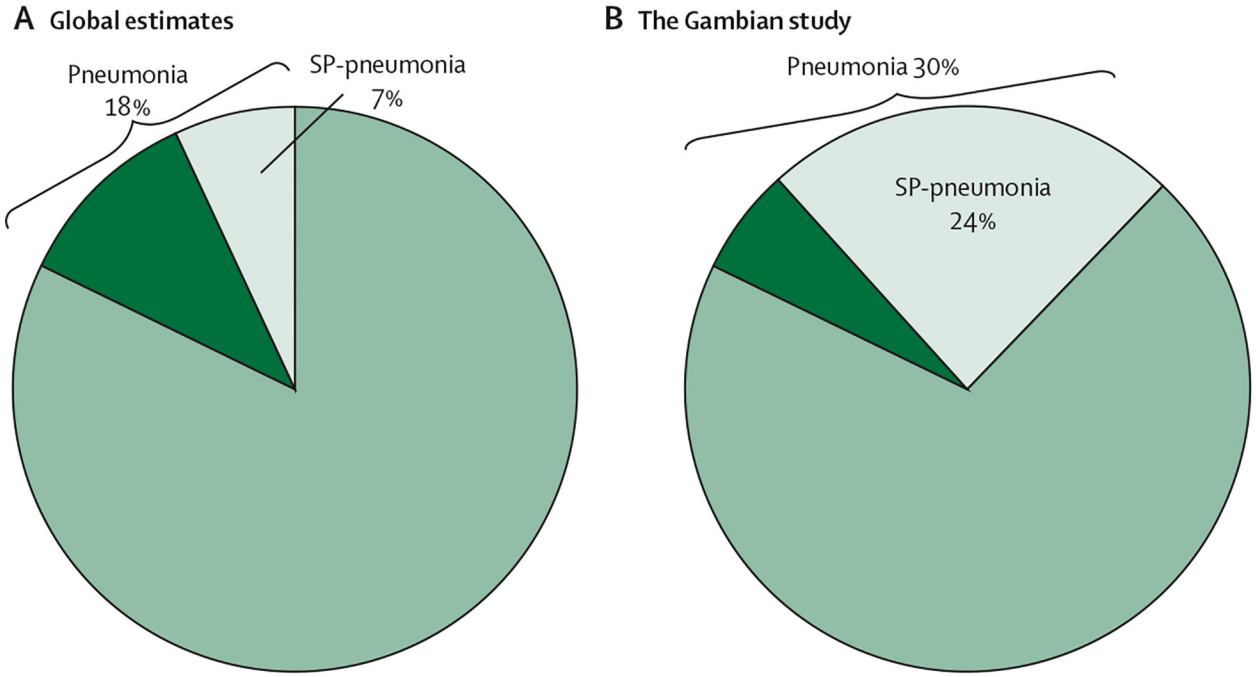

Figure 2: All-cause mortality estimates

(A) Watt and colleagues[18] estimate that, after adjustment for *Haemophilus influenzae* type B (Hib), 36% (95% CI 27–40%) of all-cause pneumonia deaths are attributable to *Streptococcus pneumoniae*. Application of this finding to the global mortality estimates presented by Liu and colleagues[7] suggests that 7% (18·3%, 95% CI 15·6–21·6%, × 36%) of global all-cause mortality is attributable to pneumococcal pneumonia. (B) Estimates of pneumococcal pneumonia mortality based on pneumococcal conjugate vaccine 9 (PCV9) studies, such as one in The Gambia,[19] are substantially higher at 24%. Pneumococcal vaccination in the Gambian study, which reduced all-serotype pneumococcal lung aspirate confirmed pneumonia by 68% (95% CI 18–89%), led to a decreased all-cause mortality of 16% (3–28%). This result suggests that, in a setting where Hib vaccinations were given to everyone, pneumococcal pneumonia accounted for 24% of all-cause mortality (100%/68% × 16%=24%). With the estimation that pneumonia accounted for 30% of all-cause mortality in this population (authors' estimate), pneumococcal pneumonia is likely to be a greater contributor to all-cause mortality than suggested by global estimates. SP=*Streptococcus pneumoniae*.

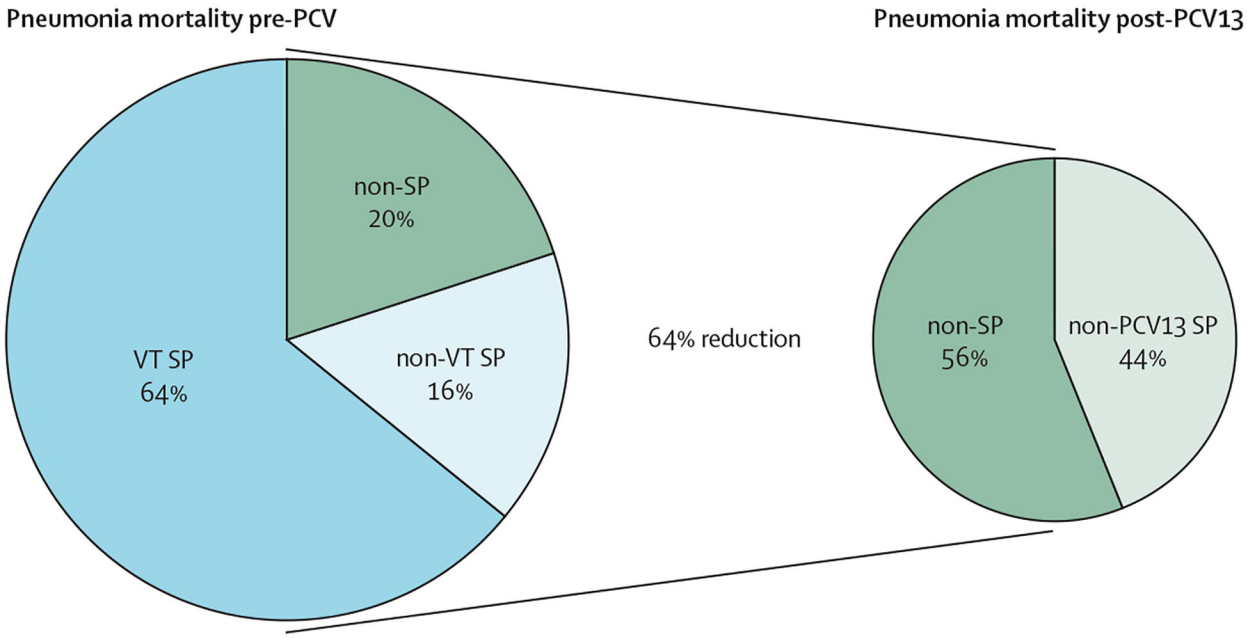

Figure 3: Reduction of pneumonia mortality and morbidity:

Pneumonia mortality before pneumococcal conjugate vaccine (PCV) assumes that pneumococcus causes 80% of pneumonia mortality (authors' estimate) with 80% of pneumococcal serotypes included in PCV9/10/13. This translates to 64% of pneumonia mortality being attributable to vaccine type pneumococcus (80% × 80%) and the remaining 16% to non-vaccine type. The actual percentage coverage of non-bacteraemic pneumonia in the Gambia study,[19] which included routine *Haemophilus influenzae* type B (Hib) vaccination, is unknown but 80% coverage with 80% efficacy (64%) is close to the 68% (95% CI 18–89%) observed effect on lung aspirate confirmed pneumococcal pneumonia.[19] With the assumption that PCV13 introduction and subsequent herd immunity will result in 80% reduction of vaccine-type pneumonia with no replacement disease, there will be a 64% reduction (80% × 80%) in pneumonia mortality after PCV13, as represented by a smaller pie chart. No residual vaccine type disease exists in this scenario. The remaining pneumonia mortality, unaffected by the introduction of PCV13, will therefore be composed of 44% non-PCV13 pneumococcal serotypes (non-VT SP/[non-VT SP+non-SP]) and 56% non-*Streptococcus pneumoniae* disease (non-SP/[non-VT SP+non-SP]). Despite best-case scenarios of pneumococcal vaccine coverage, a substantial proportion of pneumonia mortality will remain attributable to *Streptococcus pneumoniae*. The 56% of mortality not caused by pneumococcus might be partly due to viral or other emerging pathogens. SP=*Streptococcus pneumoniae*. VT=vaccine type.

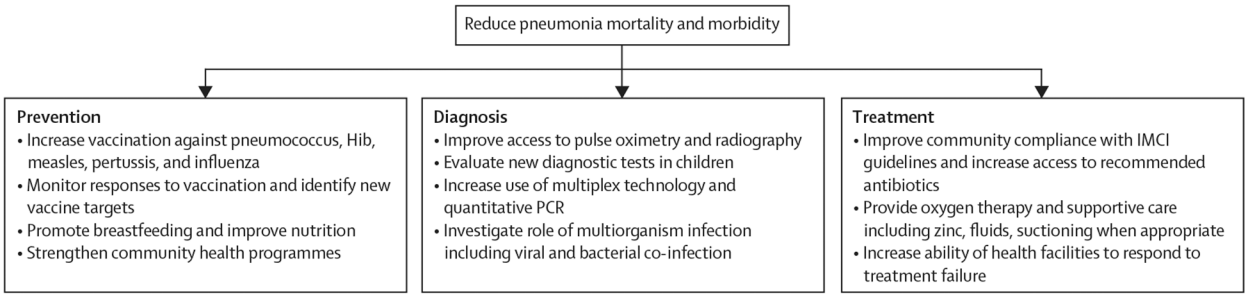

Figure 4: Model of proposed interventions for improvement of pneumonia mortality and morbidity:

Hib=*Haemophilus influenzae* type B. PCR=polymerase chain reaction. IMCI=Integrated Management of Childhood Illness.