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Prevention and Control of Childhood Pneumonia and Diarrhea

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Abstract

Pneumonia and diarrhea are the two leading infectious causes of death in children under 5 worldwide, most of which occur in low- and middle-income countries (LMICs) in sub-Saharan Africa and Southern Asia. The past decade has seen large reductions in global childhood mortality, in part due to expansion of non-specific public health interventions, as well as the roll out of vaccines against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and rotavirus in LMICs. Recent studies have shown that the leading causes of childhood diarrhea vary geographically, and include rotavirus, norovirus, *Cryptosporidium*, *Shigella*, Enterotoxigenic *Escherichia coli*, *Vibrio cholerae*, and *Campylobacter*, underlining the critical need for development of new vaccines against diarrheal pathogens. Etiological studies of childhood pneumonia are ongoing, though previous reports have identified respiratory syncytial virus, *S. pneumoniae*, *H. influenzae*, and influenza virus as prominent contributors to the global burden of disease. Further progress in this field will depend on the international community's commitment to fund and implement programs utilizing currently available vaccines, and the development of new vaccines against pathogens common to children in LMICs.

Keywords

Pneumonia; Diarrhea; Vaccines; Global Burden; Etiology

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Introduction

Pneumonia and diarrhea are the two leading infectious causes of death in children under age 5 worldwide, responsible for more than 1.5 million deaths annually. They accounted for 15% and 9%, respectively, of the 6.3 million under-five deaths that occurred globally in 2013.[1, 2] There are an estimated 1.7 billion episodes annually of diarrhea and over 150 million episodes of pneumonia. Marked decreases in mortality due to pneumonia and diarrhea over the past decade have been noted.[3] Between 2000 and 2013, there was an estimated 44% reduction in deaths due to pneumonia and 54% reduction in deaths due to diarrhea among children under 5 years.[2] Despite this, pneumonia and diarrhea continue to cause significant morbidity and mortality in young children worldwide, particularly those in Asia and Africa. Thus, efforts at optimizing prevention and control are needed. In this review, we describe strategies aimed at preventing and controlling childhood pneumonia and diarrhea.

Global burden

The World Health Organization (WHO) estimates that each year, there are >150 million cases of pneumonia in children under age 5, including 20 million cases which require hospitalization. Most of the morbidity and mortality worldwide due to pneumonia occur in low- and middle-income countries (LMICs). Using vital registration and verbal autopsy data, the Child Health Epidemiology Reference Group (CHERG) estimated the total number of pneumonia deaths in children under 5 worldwide to be approximately 935,000.[3] Up to half of deaths from pneumonia occurred in sub-Sahara Africa and approximately a third in Southern Asia. There were regional variations in the percentage of deaths attributable to pneumonia – from 5% of deaths in developed regions to 16% of deaths in sub-Saharan Africa. Most notably, 96% of episodes of pneumonia, and 99% of deaths from pneumonia, take place in LMICs.[4]

Though second to pneumonia in mortality burden, diarrheal illnesses occur more frequently. Children in LMICs under the age of 5 suffer an average of 2.9 episodes per year of diarrhea, accounting for nearly 1.7 billion episodes of diarrhea yearly,[5] resulting in over 578,000 deaths per year.[3] The peak age of diarrheal disease incidence is during infancy – from 6 to 11 months of age,[5] and the majority of deaths due to diarrhea occur in the first two years of life.[6]

Etiologies of pneumonia

Due to logistical and ethical limitations, direct sampling of infected lung tissue is not commonly performed and our knowledge of causes of pediatric pneumonia is based mostly on studies using various indirect sampling methods, such as nasopharyngeal swab, blood cultures, or induced sputum (Table 1). A large 10-country study conducted over 25 years ago revealed that respiratory viruses, especially respiratory syncytial virus (RSV), to be the leading cause of childhood pneumonia,[7] with the most common bacterial causes being *S. pneumoniae*, followed closely by *H. influenzae*. More contemporary studies have continued to identify RSV as the most common respiratory virus responsible for pneumonia worldwide, though improved molecular diagnostics have also implicated rhinovirus,

influenza virus, human metapneumovirus, and adenovirus, with significant geographic variations.[8-10] While viruses are detected in the majority of cases of pneumonia, given the high frequency of co-pathogen isolation, their contribution to severe pneumonia is unclear. Notably, a recent study from the Gambia involving lung aspirates in children under 5 years with severe pneumonia demonstrated *S. pneumoniae* to be present in 91% of lung aspirates, followed by *H. influenzae* at 23%, and *S. aureus* in 6%; in this small study, no viruses were present in >5% of samples.[11] We have also shown that the etiologies of pneumonia in children with severe acute malnutrition differ from that of well-nourished children, with Gram-negative bacteria being more common in those malnourished.[17] The PERCH (Pneumonia Etiology Research for Child Health) study, a 7-country case-control study of severe pneumonia in hospitalized children,[12] and a similar study utilizing the GABRIEL (Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income Countries) network in 9 countries,[13] are both ongoing and are expected to provide more updated and comprehensive data regarding etiology of pneumonia in LMICs.

Etiologies of diarrhea

The etiological determination of diarrheal disease and deaths are limited by the large number of pathogens present in stool of children in LMICs, even during periods of relative health. For example, Bangladeshi infants without evidence of diarrhea had an average of 4.3 enteropathogens detected, compared to an average of 0.5 in infants from the USA.[14] The past decade saw the completion of two large multi-country studies utilizing modern molecular diagnostic tools to provide insight into the etiology and consequences of acute infectious diarrhea in children of LMICs (Table 1).

The GEMS (Global Enterics Multi-Center Study), a 3-year cross-sectional case-control study, investigated the cause and incidence of moderate-to-severe diarrhea of over 22,000 children at 7 sites in Africa and Asia.[6] It found that the majority of cases were due to four pathogens: rotavirus, *Cryptosporidium*, *Shigella* spp., and heat-stable toxin producing enterotoxigenic *Escherichia coli* (ST-ETEC). Rotavirus was the top attributable cause of diarrhea in children under 24 months of age, and *Shigella* was the top cause for those 2-5 years old. Other notable pathogens among the top causes included *Vibrio cholerae*, *Campylobacter jejuni*, adenovirus 40/41, and *Aeromonas spp*, but there was substantial geographic variation.

The MAL-ED (The Interactions of Malnutrition & Enteric Infections: Consequences for Child Health and Development) project is a multi-site cohort that involved intensive surveillance for diarrhea and monthly asymptomatic stool collection from children, from birth to 24 months. Investigators found that norovirus, rotavirus, *Campylobacter*, astrovirus, and *Cryptosporidium* to be the top causes of diarrhea in the first year of life, with the addition of *Shigella spp.* in the second year.[15] These studies combine to demonstrate that bacterial, viral, and protozoal etiologies all play important roles in childhood diarrhea.

Public Health measures for prevention of childhood pneumonia and diarrhea

Pneumonia and diarrheal disease share several risk factors, including malnutrition, poor hygiene, poor socioeconomic status, lower education status, and lack of breast-feeding.[16] We have shown in a systematic review that young children with severe malnutrition are at increased risk of death from pneumonia,[17] and suffer high rates of death even after hospital discharge.[18] We have reported that severe acute malnutrition is associated with concurrent pneumonia and diarrhea; children with both illnesses have an >80-fold increased risk of death compared to those with diarrhea alone.[19] Inpatient nutritional rehabilitation of malnourished children has been demonstrated to dramatically reduce case fatality rates, especially when implemented in units with standardized protocols and trained staff.[20, 21] Interventions employed in such units include appropriate rehydration therapy, targeted feeding, empiric antibiotics directed against gram negative organisms, vitamin A supplementation, and management of hypoglycemia. Of the nutritional supplementation interventions studied, preventative zinc supplementation has been shown to reduce the incidence of diarrhea and pneumonia by over 20%, and all-cause mortality by 18% among children 12 to 59 months of age.[22] Additionally, exclusive breastfeeding of infants reduces deaths due to both pneumonia and diarrhea,[23] especially in the first 6 months of life.[24, 25]

Diarrheal diseases have long been associated with ingestion of contaminated food and water. With the increasing recognition of viral etiologies of both pneumonia and diarrhea that may be transmitted person-to-person, efforts have also focused on strategies to improve water, sanitation, and hygiene (WASH) at the household level. Interventions such as the encouragement of hand washing with soap, improving water quality, and proper disposal of excreta have all been demonstrated to reduce diarrheal burden.[26] There are limited data behind the prevention of pneumonia through WASH interventions,[27] though a recent estimate suggested that hand washing with soap could prevent over 600,000 deaths from diarrhea and pneumonia combined.[28]

The aforementioned preventive and protective measures form the backbone of public health efforts for children in LMICs. The marked reductions in mortality in the past decade have been in large part due to such non-specific interventions. The remainder of this review focuses on the use of preventive vaccines for diarrheal and respiratory pathogens. Conjugate vaccines for *H. influenza* type B and *S. pneumoniae* and rotavirus vaccines have significantly decreased the burden of pneumonia and diarrhea in high-income countries (HICs). The uptake of these vaccines and the potential development of new vaccines are expected to further enhance the reductions in childhood mortality in LMICs.

Vaccines to prevent childhood pneumonia

Children under the age of 2 years bear a large burden of bacterial respiratory infections, and polysaccharide antigens are poorly immunogenic in such children. The development of polysaccharide-protein conjugate vaccines has dramatically enhanced the prevention of pneumonia worldwide. Conjugate vaccines take advantage of a carrier protein to elicit a T cell-dependent antibody response to bacterial polysaccharide antigens. Conjugate vaccines

against S. pneumoniae and H. influenzae type B, the top two causes of bacterial lower respiratory tract infections worldwide are highly effective. Vaccines against the influenza virus are available but not widely used in LMICs, and no vaccine is yet available against RSV, the most common cause of viral pneumonia.

Vaccines against Streptococcus pneumonia (pneumococcus)

The development of a pneumococcal vaccine that is effective in young children has been of great benefit to children worldwide. Available pneumococcal vaccines include 7, 9, 10, 11, 13, and 15-valent conjugate vaccines, and a 23-valent polysaccharide (non-conjugated) vaccine. Currently used conjugate vaccines worldwide include the 13-valent conjugate vaccines (PCV13), which uses CRM197 (diphtheria toxin mutant) as a carrier, and the 10-valent conjugate (PCV10), which uses three proteins: the diphtheria toxoid, the tetanus toxoid, and non-typeable H. influenzae protein D.

Pneumococcal conjugate vaccines prevent invasive pneumococcal disease (IPD), including meningitis, sepsis, and otitis media as well as pneumococcal pneumonia. In a meta-analysis that included six randomized controlled trials conducted in children under two years in Africa, US, Philippines, and Finland, the pooled efficacy of PCV7 was 80% for vaccine-serotype associated IPD, and 58% for all-serotype IPD. The effect of PCV7 on pneumonia was lower – the pooled efficacy for radiologically defined pneumonia was 27% and for clinical pneumonia 6%.[29] This likely reflects the importance of other pathogens in addition to S. pneumonia in childhood pneumonia. Several studies have suggested additional benefits of PCV beyond prevention of pneumococcal pneumonia in those vaccinated, including prevention of viral-attributed pneumonia,[30] reduction in IPD in older unvaccinated age groups due to herd immunity,[31] and serotype-associated IPD in younger unvaccinated age groups.[32]

The introduction of pneumococcal conjugate vaccines has had substantial impact on the burden of pneumococcal disease in every country where it has been widely adopted. The impact may be higher among young children in LMICs than those in HICs. A meta-analysis of serotypes causing IPD worldwide estimated that 49-88% of pneumococcal deaths in Africa and Asia are caused by serotypes covered in in PCV10 and PCV13.[33] Since 2006, the WHO has recommended that PCV be included in all routine immunization programs.

The uptake of PCV in LMICs has been limited, however, in large part due to the high cost of PCV. In response to this, GAVI (Global Alliance for Vaccines and Immunization) has worked to accelerate the introduction of PCVs in LMICs by working with manufacturers to commit supply and ensuring predictable vaccine pricing for the PCV10 and PCV13 vaccines. In total, more than 125 countries, including 50 Gavi-supported countries, have introduced universal PCV to their immunization programs, though >50% of the world's infants still do not have access to PCV,[34] most notably many of those living in Asian LMICs.

Large randomized studies of 10- and 13-valent PCVs have not been conducted in LMICs, and their effectiveness is inferred from comparable immunogenicity as PCV7. With the use of PCV7, surveillance studies in high-income countries demonstrated a plateau in the

reduction of pneumococcal infection rates in some populations due to serotype.[35] Notably, there are more than 90 pneumococcal serotypes. Although the factors that drive the epidemiology of *S. pneumoniae* are complex and poorly understood, further serotype replacement seems likely. Vaccines aimed at inducing serotype-independent immunity are in early stages of development and hold promise of not being subject to serotype replacement.[36]

Vaccines against Haemophilus influenzae type b (Hib)

As with pneumococcal vaccines, the first Hib vaccines were polysaccharide formulations that were poorly immunogenic in young children.[37] However, since 1987, a number of Hib conjugate vaccines (HibCVs) have become available, including ones conjugated to an outer membrane vesicle of *Neisseria meningitidis*, one conjugated to tetanus toxoid, and HiBCVs have been combined with other childhood vaccines. Initial RCTs of HibCVs showed >95% efficacy against invasive disease,[38] and introduction of HibCV has nearly eliminated invasive Hib disease from countries where the vaccine is widely used, including countries in sub-Saharan Africa.[39]

In 2006, the WHO issued a recommendation for the adoption of HibCVs in routine immunization programs worldwide. In response to the slow uptake of HibCV in LMICs, the Hib initiative was launched by GAVI to disseminate of data regarding burden of disease, and provide advocacy for its introduction in low-income countries. Currently, over 190 countries have introduced a Hib-containing vaccine into their National Immunization Program,[34] including all 73 Gavi countries. However, it is estimated that over a third of infants worldwide are still not reached by the current immunization coverage.[34]

Vaccines against influenza virus

Despite the large burden of respiratory illness due to influenza virus infection among young children, and the longstanding availability of the influenza vaccine in high income countries, vaccines against influenza have not been widely implemented in any LMICs. The biggest reason is likely the cost and logistical resources needed to implement yearly immunizations. Inactivated influenza vaccines (IIV) are produced to match influenza strains that circulate at the end of the last season. Efficacy is dependent on degree of matching to actual circulating strains, and studies evaluating IIVs in children are limited. In a recent large multi-country RCT, a quadrivalent IIV had an efficacy of 60%.[40] On the other hand, the single-dose live attenuated influenza vaccine (LAIV) holds promise to be an effective and less costly option for LMICs. In contrast to IIVs, a large number of RCTs have shown that LAIVs are effective in preventing influenza illness in young children.[41] Furthermore, there is evidence that LAIVs may have activity against mismatched strains, and possibly provide longer duration of protection than inactivated influenza vaccines. A cost-effectiveness analysis conducted in Thailand showed that vaccination with LAIV to be highly cost-effective, more than for IIV vaccine.[42] Current research efforts are focused on the feasibility of influenza vaccine implementation,[43] as well as the protection of infants through vaccination during pregnancy.[44]

Vaccines to prevent childhood diarrhea

Currently, there are few vaccines available for prevention of childhood diarrhea. The rotavirus vaccine, highly efficacious and widely available in most high-income countries, has shown lower efficacy in some LMICs. Efforts to include it in national immunization programs have been slow. Recent enhancement and development of the oral cholera vaccine has increased its availability and the WHO now recommends it for use in both endemic and epidemic areas. We will review these two available vaccines below. Vaccines against norovirus, Shigella, and ETEC are in advanced stages of development, and given the surprisingly high burden of illness caused by Cryptosporidium, efforts are underway to increase our understanding of its host-pathogen relationship that could allow development of effective vaccines.

Vaccines against rotavirus

Rotavirus is the most common cause of diarrhea in the first year of life,[6] which is the age with the highest incidence of, and deaths due to, diarrheal illness. The WHO has recommended that rotavirus vaccine for infants be included in national immunization programs. Two live attenuated oral rotavirus vaccines are available worldwide – a 3-dose pentavalent human-bovine re-assortment vaccine containing serotypes G1, G2, G3, G4 and P1[8] (RV5), and a 2-dose monovalent vaccine derived from serotype combination G1P[8] (RV1), which likely has cross-protection against most other serotypes.

A number of studies have shown that both rotavirus vaccines are effective in preventing gastroenteritis due to rotavirus in a variety of geographical settings. In large placebo-controlled studies of RV5 and RV1,[45, 46] the vaccines were associated with approximately 90% efficacy against incidence of, hospitalization for, and emergency visits due to severe rotaviral gastroenteritis. Rotavirus vaccine has also been associated with decrease in all-cause gastroenteritis and indirect protection of unvaccinated older siblings.[47] A total of 79 countries have introduced a rotavirus vaccine into their National Immunization Program, though an estimated three-quarters of the world's infants still do not have access to the rotavirus vaccine,[34] including most infants living in South and Southeast Asia.

Currently available rotavirus vaccines have lower immunogenicity and effectiveness in LMIC settings than seen in studies from North America, Europe, and South America. Large multi-country studies from Sub-Saharan Africa[48, 49] and Asia[50] showed vaccine efficacy estimates of 40-50%, a substantial lower number. Issues regarding immunogenicity, and the possible deleterious effect of environmental enteropathy, malnutrition, and alterations in gut microbiota, are currently being examined in the multi-site birth cohort PROVIDE (Performance of Rotavirus and Oral Polio Vaccines in Developing Countries) study.[51] Adjunctive interventions may be needed to optimize the delivery and efficacy of rotavirus and other oral vaccines in developing countries.

Vaccines against *Vibrio cholerae*

Despite being available for several decades, vaccines against cholera have not been widely used in endemic countries due to concerns regarding efficacy, duration of protection, and

costs. Recently, in efforts spearheaded by the International Vaccine Initiative (IVI), an existing oral cholera vaccine (OCV) produced and originally implemented in Vietnam was enhanced to meet WHO prequalification standards and licensed in India. This vaccine, Shanchol, is a bivalent (O1 and O139) heat- and formalin-killed whole cell *V. cholerae* vaccine, given as 2 doses 14 days apart. Unlike its precursor Dukoral, it does not contain a recombinant cholera toxin subunit. In a large double-blind cluster-randomized placebo-controlled trial in Kolkata, India, the vaccine was found to have a protective efficacy of 65% at 5 years of follow-up.[52]

In 2011, the WHO recommended that OCVs be used in both endemic and epidemic settings, and in 2012, in response to recent epidemics such as in Haiti and sub-Saharan Africa, the WHO established a global stockpile of OCV. Despite the high burden of cholera in young children,[53] OCVs have a lower protective efficacy and a shorter duration of protection in young children under 5 years of age than in older persons.[54] The reasons for this are not fully understood. We have shown that children 24-59 months mount lower *V. cholerae* polysaccharide-specific responses to OCV than older children and adults.[55] Given the logistical difficulties of completing a multiple-dose regimen in settings where cholera is present, efforts to study alternative dosing schedules of currently available OCVs are underway, and several single-dose live attenuated oral cholera vaccines are under development.[56]

Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea

Despite the availability of effective cost-effective interventions to end preventable childhood deaths from diarrhea and pneumonia, access is low in many LMICs.[57] There are many barriers to the implementation and scale-up of interventions to end preventable deaths in children from pneumonia and diarrhea (Table 2).[58,59] Following a series of regional and country workshops and subsequent follow-up and feedback from health care workers, the WHO conceptualized a “protect, prevent, and treat” framework to reduce morbidity and mortality from pneumonia and diarrhea in LMICs.[59] In 2013, the WHO and The United Nations Children’s Fund (UNICEF) launched the Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea (GAPPD) with a goal to eliminate child deaths from pneumonia and diarrhea by 2025.[60] Community-based delivery platforms have been proposed to reach the poorest, hard to reach populations and reduce health care inequalities.[16]

Progress has been made in improving access to childhood vaccines to prevent pneumonia and diarrhea. Given the various challenges in modern vaccine development (e.g. lack of investments, decreasing number of vaccine manufacturers), establishment of a Global Vaccine-Development Fund has been proposed.[61] Most experts in the field envision that GAPPD goals can be achieved, though successful implementation of the WHO/UNICEF Integrated GAPPD will need strong commitment from national governments, private sector and other stakeholders.[59]

Conclusions

Despite marked reductions in the past decade, pneumonia and diarrhea continue to be the leading killers of young children worldwide. There are now a number of effective and relatively low-cost interventions to control these diseases, and organizations such as GAVI have enabled many countries to implement pathogen-specific vaccines into their National Immunization Programs. Effective vaccines are needed against other major killers of children including RSV, ETEC and norovirus. Further progress in this field will continue to depend on international commitment to fund, communicate, and advocate for the needs of these children.

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Key Points

- Pneumonia and diarrhea are the two major preventable causes of childhood deaths in young children in low- and middle-income countries.
- Public health interventions, including nutritional rehabilitation, zinc supplementation, exclusive breastfeeding, and WASH strategies, have all contributed towards marked reductions in mortality; however, current coverage of these cost-effective interventions remains low.
- Respiratory syncytial virus (RSV), *Streptococcus pneumoniae* and *Haemophilus influenza* are the leading causes of childhood pneumonia, the latter two of which can be prevented through vaccination
- Vaccines against diarrheal pathogens include that against cholera and rotavirus, and development of vaccines against other leading causes of diarrhea, such as norovirus, *Cryptosporidium*, *Shigella*, *Campylobacter*, and Enterotoxigenic *Escherichia coli*, are urgently needed
- Successful implementation of the WHO/UNICEF Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea will need strong commitment from national governments, private sector and other stakeholders

Table 1

Top pathogens causing childhood pneumonia and diarrhea

Pneumonia [8-11]	**Diarrhea** [6,15]
Bacterial	Bacterial
Streptococcus pneumoniae *	*Shigella*
Haemophilus influenzae *	Enterotoxigenic *Escherichia coli*
Mycoplasma pneumonia	*Campylobacter*
Staphylococcus aureus	*Aeromonas*
	Vibrio cholerae *
Viral	
Respiratory syncytial virus	Viral
Influenza A or B virus*	Rotavirus*
Human rhinovirus	Norovirus
Human metapneumovirus	Astrovirus
Adenovirus	Adenovirus
Parainfluenza virus	
	Protozoal
	Cryptosporidium

* = vaccine available

Table 2

Barriers to the implementation and scale-up of pneumonia and diarrhea interventions*

- Lack of specific policy guidance for child health, CCM or use of antibiotics and other essential health commodities by CHW
- Lack of harmonization, coordination and collaboration between programs and sectors
- Insufficient involvement with the private sector
- Suboptimal vaccine coverage
- Financial constraints
- Scarcity of human resources
- Lack of adequate training for health care providers
- Lack of adequate health commodities and supplies (e.g. antibiotics, zinc, vaccines)
- Health care access issues due to geographical and financial barriers
- Poor surveillance
- Inadequate monitoring and evaluation

* Data from Qazi S, Aboubaker S, MacLean R, et al. Ending preventable child deaths from pneumonia and diarrhea by 2025: The Integrated Global Action Plan for Pneumonia and Diarrhea. Arch Dis Child 2015;100(Suppl 1):s23-s28

Abbreviations: CCM, community case management; CHW, community health workers;

Table 3

WHO/UNICEF Framework for protection, prevention, and treatment of pneumonia and diarrhea to reduce morbidity and mortality*

PROTECT Children by Establishing Good Health Practices From Birth

- Exclusive breastfeeding for 6 months
- Adequate complementary feeding
- Vitamin A supplementation

PREVENT Children from Becoming Ill from Pneumonia and Diarrhea

- Vaccines: Hib, PCV, pertussis, measles and rotavirus
- Handwashing with soap
- Safe drinking water and sanitation
- Reduce household air pollution
- HIV prevention
- Cotrimoxazole prophylaxis for HIV-infected and exposed children

TREAT Children who are ill from pneumonia and diarrhea with appropriate measures

- Improved care seeking and referral
- Case management at the health facility and community level
- Supplies: Low osmolarity ORS, zinc, antibiotics, and oxygen
- Continued feeding (including breastfeeding)

Abbreviations: HiB, *Haemophilus influenzae* vaccine; PCV, pneumococcal conjugate vaccine; ORS, oral rehydration salts, UNICEF, United Nations Children's Fund; WHO, World Health Organization;

From WHO/UNICEF. Ending preventable child deaths from pneumonia and diarrhea by 2025: The Integrated Global Action Plan for Pneumonia and Diarrhea. Geneva. WHO, 2013; with permission.