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Relevant Websites

http://endabuse.org/ – Family Violence Prevention Fund.

http://www.nctsnet.org/nccts/nav.do?pid=typ_mt_ptlkt – National Child Traumatic Stress Network, Pediatric Medical Traumatic Stress Kit for Health Care Providers.

http://www.nccpr.org/index_files/page0007.html – National Coalition for Child Protection Reform, Summary of Expert Testimony on the Impact of Children of Witnessing Domestic Violence.

http://www.ojp.usdoj.gov/ovc/assist/cwwv.htm – U.S. Department of Justice, Office for Victims of Crime.

Childhood Infectious Diseases: Overview

Z A Bhutta and M A Saeed, The Aga Khan University, Karachi, Pakistan

Introduction

In the late twentieth century, substantial reductions in child mortality occurred in low- and middle-income countries. The fall in child deaths during 1960–90 averaged 2.5% per year and the risk of dying in the first 5 years of life halved – a major achievement in child survival. In the period 1990–2001, the rate of mortality reduction averaged 1.1% annually, mostly after the neonatal period. Most neonatal deaths are unrecorded in formal registration systems and communities with most neonatal deaths have the least information related to mortality rates and interventions. Not surprisingly, therefore, current global burden figures of newborn and young infant deaths are largely estimates. These figures suggest that 10.6 million children under 5 years die annually and of the 130 million births, 3.8 million die in the first 4 weeks of life – the neonatal period, with three-quarters of neonatal deaths occurring in the first week after birth. The south-East Asian region accounts for the highest number of child deaths (3 million), whereas the highest mortality rates are seen in sub-Saharan Africa. Annually, sub-Saharan Africa and South Asia share 41% and 34% of child deaths, respectively (**Table 1**). Surprisingly, only six countries account for half of worldwide deaths and 42 for 90% of child deaths. The predominant causes are pneumonia, diarrhea, and neonatal disorders with additional contribution from malaria and AIDS (see **Tables 2** and **3** for details). In all, 99% of neonatal deaths occur in poor countries (estimated average neonatal mortality rate (NMR) of 33/1000 live births), while the remainder occur in 39 high-income countries (estimated NMR of 4/1000 live births).

Determinants of Child Health and Mortality: A Social Perspective

A number of social determinants contribute to the high burden of infectious diseases in developing countries. These include distal determinants such as income, social status, and education, which work through an intermediate level of environmental and behavioral risk factors (**Figure 1**). These risk factors, in turn, lead to the proximal causes of death (nearer in time to the terminal event), such as undernutrition, infectious diseases, and injury. The major social determinants affecting the under 5 years' mortality and morbidity include poverty, malnutrition, inequity, lack of education, failure to implement the breast-feeding and complementary feeding programs, the presence of debilitating disease in addition to infections, complications of labor and low birth weight, and inadequate health-related social behaviors and practices and other social and cultural determinants of health. A detailed description of each determinant is beyond the scope of this article.

The Role of Infectious Disease in Child Health and Mortality

The World Health Organization's (WHO) work on the global burden of disease, consistent with the International Classification of Diseases (ICD), stipulates one cause of death, considered to be the "disease or injury which initiated the train of morbid events leading directly to death." The risk of neonatal death from infection in very high-mortality countries is about 11-fold higher than in low-mortality countries. Major categories of neonatal deaths in poor communities include preterm birth (28%), severe infections (36%) (sepsis/pneumonia [26%], tetanus [7%], diarrhea [3%]), and complications of asphyxia (23%). Of the remaining 14%, half are related to congenital abnormalities (see **Figures 2** and **3**).

Four million babies die in the neonatal period and a similar number are stillborn. Around 99% of deaths occur in the developing countries (average NMR of 33), and about half occur at home. In poor communities many deaths are unrecorded, indicating the perceived inevitability of their deaths. Globally, neonatal deaths account for 38% of deaths in children aged under 5 years.

Table 1 Regional classification of mortality rates and causes of death in children under 5 years

Region	< 5 mortality rate per 1000 live births (2004)	Infant mortality rate per 1000 live births (2004)	Neonatal mortality rate per 1000 live births (2000)	Cause of death among children under 5 years					
				Neonatal causes (2000)	HIV/AIDS (2000)	Diarrhea (2000)	Malaria (2000)	Pneumonia (2000)	Other (2000)
African region	167	100	43	26.2	6.8	16.6	17.5	21.1	5.6
Americas region	25	21	12	43.7	1.4	10.1	0.4	11.6	27.9
South-East Asia region	77	56	38	44.4	0.6	20.1	1.1	18.1	9.9
European region	22	18	11	44.3	0.2	10.2	0.5	13.1	25.4
Eastern Mediterranean region	94	69	40	43.4	0.4	14.6	2.9	19.0	13.5
Western Pacific region	31	25	19	47.0	0.3	12.0	0.4	13.8	18.4

World Health Organization (WHO) (2006) Working together for health. *World Health Report*. Geneva: WHO.

Table 2 Global burden of diseases: Deaths and DALYs[a] 2001[d]

	Low and middle income		High income		World	
	Deaths	DALYs (3,0)[b]	Deaths	DALYs (3,0)[b]	Deaths	DALYs (3,0)[b]
All causes: total number (thousands)	48 351	1 386 709	7891	149 161	56 242	1 535 871
Rate per 1000 population	9.3	265.7	8.5	160.6	9.1	249.8
Age-standardized rate per 1000[c]	11.4	281.7	5.0	128.2	10.0	256.5
Selected cause groups	*Number in thousands (%)*					
Communicable diseases	17 613 (36.4)	552 376 (39.8)	552 (7.0)	8561 (5.7)	18 166 (32.3)	560 937 (36.5)
HIV/AIDS	2552 (5.3)	70 796 (5.1)	22 (0.3)	665 (0.4)	2574 (4.6)	71 461 (4.7)
Diarrhea	1777 (3.7)	58 697 (4.2)	6 (<.1)	444 (0.3)	1783 (3.2)	59 141 (3.9)
Malaria	1207 (2.5)	39 961 (2.9)	0 (0.0)	9 (<.1)	1208 (2.1)	39 970 (2.6)
Lower respiratory infections	3408 (7.0)	83 606 (6.0)	345 (4.4)	2314 (1.6)	3753 (6.7)	85 920 (5.6)
Perinatal conditions	2489 (5.1)	89 068 (6.4)	32 (0.4)	1408 (0.9)	2522 (4.5)	90 477 (5.9)
Protein-energy malnutrition	241 (0.5)	15 449 (1.1)	9 (0.1)	130 (<.1)	250 (0.4)	15 578 (1.0)

DALY, Disability-adjusted life year.

[a]Numbers in parentheses indicate percentage of column total. Broad group totals are additive but should not be summed with all other conditions listed in table.

[b]DALYs (3,0) refer to the version of the DALY based on a 3% annual discount rate and uniform age weights.

[c]Age-standardized using the WHO World Standard Population.

[d]Includes only causes responsible for more than 1% of global deaths or DALYs in 2001.

Table 3 World leading causes of DALYs[a] in 2000

All causes	Rank	% of total
Lower respiratory infections[b]	1	6.4
Perinatal conditions[b]	2	6.2
HIV/AIDS	3	6.1
Diarrheal diseases[b]	5	4.2
Malaria	9	2.7

DALY, Disability-adjusted life year.

[a]DALYs indicate time lived with disability and time lost due to premature mortality.

[b]Primarily or exclusively childhood diseases (<5 yrs).

Issues in Presentation

Eighteen million babies are estimated to be born with low birth weight (LBW) (under 2.5 kg at birth) every year, with half in south Asia. LBW is due to short gestation (preterm birth) or *in utero* growth restriction, or both. Prematurity, asphyxia, and *in utero* growth restriction are also indirect causes or risk factors for neonatal deaths, especially during childbirth or the first week of life. The increased risk of death among LBW infants may persist for all of infancy and, indeed, may carry long-term consequences.

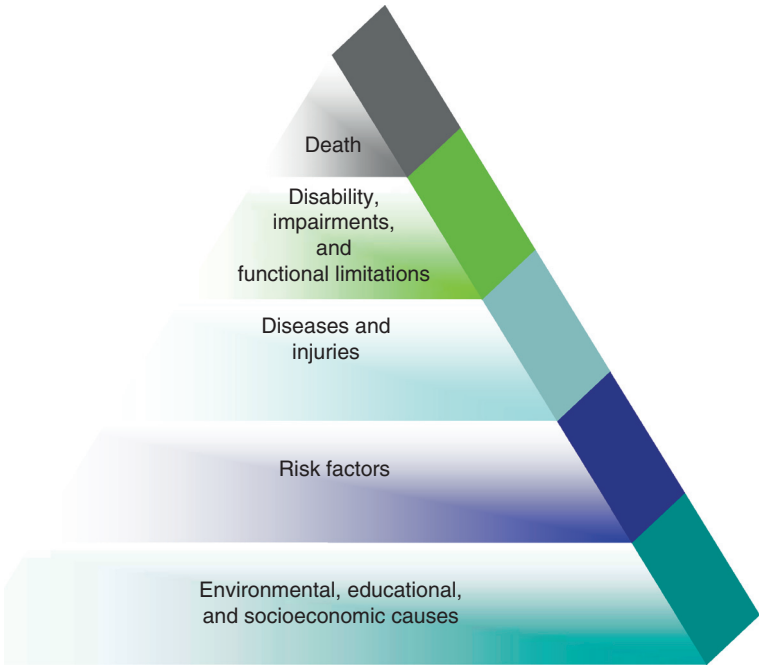

Figure 1 Overview of the burden of disease framework. This diagram is intended for a broader scale. For example, environmental factors can be an underlying factor of to the causes of death but injuries can directly cause disability or death.

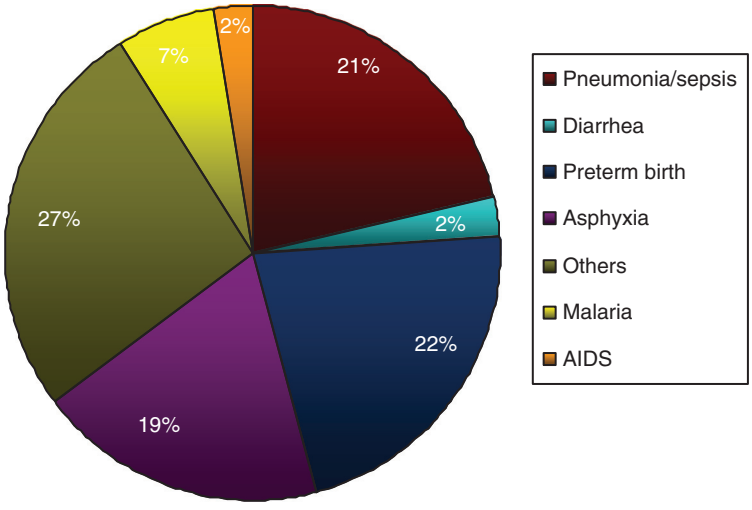

Figure 2 Percentage distribution of cause-specific mortality among neonates. Reproduced with permission from Lawn JE, Cousens S, Zupan J (2005) Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? *Lancet* 365: 891–900.

Implications for Public Health

The relative importance of different causes of death varies with NMR. So, too, varies the number of births assisted by a skilled attendant and the proportion of births within a health facility. Since neonatal deaths account for 24 to 56% of deaths in children under 5 years everywhere, no region can afford to ignore them. Further reductions in child mortality will depend on substantially improving neonatal survival. Reductions of up to 70% of neonatal deaths can be achieved if proven interventions are implemented effectively with high coverage in populations of highest need. Table 4 summarizes known maternal and newborn interventions that can improve newborn survival.

Neonatal Sepsis and Meningitis

Sepsis and meningitis are significant causes of newborn morbidity and mortality, particularly in preterm, LBW infants. Neonatal sepsis may be defined both clinically (Table 5) and microbiologically, by positive blood and/or cerebrospinal fluid cultures. It may also be classified as either early-onset sepsis (EOS) or late-onset sepsis (LOS). Meningitis can occur as a part of either EOS

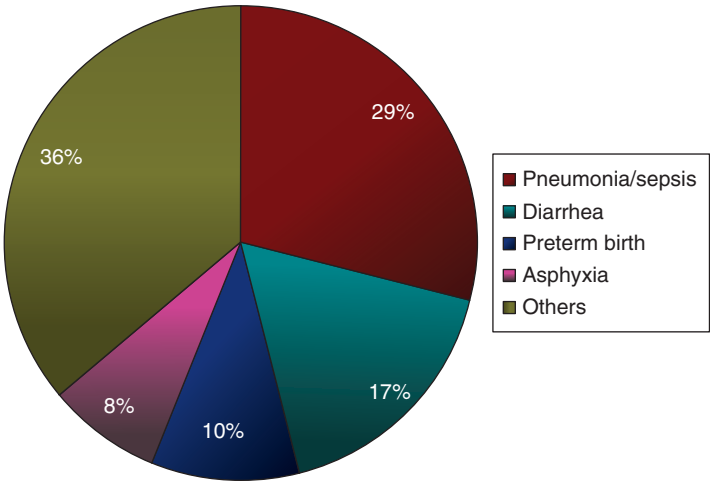

Figure 3 Percentage distribution of cause-specific mortality in children under 5 years. Reproduced with permission from Black RE, Morris SS, Bryce J (2003) Where and why are 10 million children dying every year? *Lancet* 361: 2226–2234.

Table 4 The salient maternal and newborn interventions that increase newborn survival

Maternal interventions	*Level of evidence*	*Newborn interventions*	*Level of evidence*
Antenatal			
Clean delivery practices	Clear evidence[a]	Pneumonia case management	Clear evidence[a]
Syphilis screening and treatment	Clear evidence	Newborn resuscitation	Some evidence[b]
TT immunization	Clear evidence	Prevention and management of hypothermia	Some evidence
Maternal schooling/health education	Some evidence[b]		
Antenatal care package(s)	Some evidence	Prevention and management of hypoglycemia	Some evidence
Balanced protein-energy supplementation	Some evidence		
Periconceptional folate supplementation	Some evidence	Prevention of ophthalmia neonatorum	Some evidence
Iodine supplementation	Some evidence		
Malaria treatment and chemoprophylaxis, IPT and ITNs	Some evidence	Hepatitis B vaccination	Some evidence
		Topical emollient therapy	Some evidence
Deworming	Some evidence	Neonatal care packages	Some evidence
Antibiotics for PPROM	Some evidence	Care in peripheral health facilities	Some evidence
Traditional birth attendant/CHW training	Some evidence		
Maternal care packages	Some evidence		
Intrapartum			
Maternal vaginal and newborn skin antisepsis	Some evidence		
After childbirth			
Breast feeding	Clear evidence		
Kangaroo mother care (low-birth-weight infants in health facilities)	Clear evidence		

Abbreviations: CHW, community health workers; IPT, intermittent preventive treatment; ITN, insecticide-treated bed net; PPROM, preterm prolonged rupture of membranes; TT, tetanus toxoid.

[a]Evidence of efficacy and effectiveness. Interventions of incontrovertible efficacy and which seem feasible for large-scale implementation based on effectiveness trials.

[b]Interventions effective in reducing perinatal or neonatal mortality, or primary determinants thereof, but there is a lack of data on effectiveness in large-scale program conditions.

or LOS, or as focal infection with late-onset disease. The distinction has clinical relevance, as EOS is mainly due to bacteria acquired before and during delivery, and LOS, to bacteria acquired after delivery (nosocomial or community sources). In the literature, however, there is little consensus as to what age limits apply, with EOS ranging from 48 hours to 6 days after delivery.

Serious infections cause an estimated 30 to 40% of neonatal deaths, especially in rural populations, and are associated with several risk factors. The proportion of deliveries assisted by a skilled attendant is low in most such circumstances, ranging from 37 to 69% in Africa and 29 to 66% in Asia.

Survival of neonatal meningitis relates to factors such as age, time, and clinical stability before effective antibiotic treatment; the exact microorganism and number of bacteria or quantity of active bacterial products in the cerebrospinal fluid (CSF) at the time of diagnosis; intensity of the child's

inflammatory response; and time required to sterilize CSF cultures through antibiotic treatment. The highest rates of mortality and morbidity occur following meningitis in the neonatal period.

Global and Regional Epidemiology

Severe bacterial infections are responsible for 460 000 deaths annually, in addition to an additional 300 000 fatalities from tetanus. Although maternal tetanus vaccination during pregnancy reduces rates of neonatal tetanus, contamination of the umbilical cord stump after delivery with tetanus spores continues to be a core problem. The reported incidence of neonatal sepsis varies from 7.1 to 38 per 1000 live births in Asia, from 6.5 to 23 per 1000 live births in Africa, from 3.5 to 8.9 per 1000 live births in South America and the Caribbean, and from 6 to 9 per 1000 in the United States and Australia. The incidence of neonatal meningitis is 0.1 to 0.4 per 1000 live births, and higher in developing countries. Despite major advancements in neonatal care, overall case-fatality rates (CFR) from sepsis range from 2% to as high as 50%.

The WHO's recommended clinical criteria for diagnosing sepsis and meningitis in neonates are shown in Table 5. The organisms causing sepsis and meningitis, respectively, in developing and developed countries are given in Table 6.

Table 5 WHO's recommended clinical criteria for diagnosing sepsis and meningitis in neonates[a]

Sepsis	*Meningitis*
Symptoms	*General signs*
Convulsions	Drowsiness
Inability to feed	Reduced feeding
Unconsciousness	Unconsciousness
Lethargy	Lethargy
Fever (>37.7 °C or feels hot)	High-pitched cry
Hypothermia (<35.5 °C or feels cold)	Apnea
Signs	*Specific signs*
Severe chest in-drawing	Convulsions
Reduced movements	Bulging fontanelle
Crepitations	
Cyanosis	

[a]The more symptoms a neonate has, the higher the probability of disease.

The Nosocomial Pathway

Unfortunately, hospitals in developing countries are also hotbeds of infection transmission, especially multidrug, antibiotic-resistant, hospital-acquired infection. Reported rates of neonatal sepsis vary from 6.5 to 38 per 1000 live hospital-born babies, and the rates of bloodstream infection range from 1.7 to 33 per 1000 live births, with rates in Africa clustering around 20 and in South Asia around 15 per 1000 live births (Table 7).

Evidence-Based Interventions to Address Neonatal Infections

Child survival and safe motherhood strategies have yet to adequately address neonatal mortality. The fourth Millennium Development Goal (MDG-4) commits the international community to reducing mortality in children aged under 5 years by two-thirds from 1990 base figures by 2015. Real progress in saving newborns will

Table 6 The organisms causing sepsis in the developing and developed countries

Neonatal sepsis		*Neonatal meningitis*	
Developing countries	*Developed countries*	*Developing countries*	*Developed countries*
Gram-negative organisms (more common)	*Gram-negative organisms*	*Gram-negative organisms (more common in <1wk)*	*Gram-negative organisms*
Klebsiella *Escherichia coli* *Pseudomonas* *Salmonella*	*Escherichia coli* (more common)	*Klebsiella* *Escherichia coli* *Serratia marscesens* *Pseudomonas* *Salmonella Listeria monocytogenes*	*Escherichia coli* *Listeria monocytogenes*
Gram-positive organisms (less common)	*Gram-positive organisms*	*Gram-positive organisms*	*Gram-positive organisms*
Staphylococcus aureus Coagulase-negative staphylococci (CONS) *Streptococcus pneumoniae* *Streptococcus pyogenes*	Group B *Streptococcus* (GBS) (more common) Coagulase-negative staphylococci (CONS) *Staphylococcus aureus*	*Streptococcus pneumoniae* (more common in < 1wk) Coagulase-negative staphylococci (CONS) *Staphylococcus aureus*	Group B *Streptococcus* (GBS) *Streptococcus pneumoniae*

depend upon provision of a good mix of preventive and therapeutic services.

Preventive Measures

Preventive interventions need to bridge the continuum of care from pregnancy, through childbirth and the neonatal period, and beyond. Lack of positive health-related behavior, education, and poverty is an underlying cause of many neonatal deaths, either through increasing the prevalence of risk factors such as maternal infection, or through reducing access to effective care.

Attempts to reduce LBW births at the population level have had limited success. Many deaths in preterm and LBW babies can be prevented with extra attention to warmth, feeding, and prevention or early treatment of infections. In developing countries, 90% of mothers deliver at home without skilled birth attendants present. Simple low-cost interventions, notably tetanus toxoid vaccination, exclusive breast feeding, counseling for birth preparedness, and breast-feeding promotion through peer counselors and women's groups have been shown to reduce newborn morbidity and mortality. Postnatally 'kangaroo' mother care for LBW infants (where babies are carried next to the mother's chest for warmth), hand washing and decreased congestion in medical facilities, attention to environmental hygiene and sterilization, and antibiotics for neonatal infections are additional health system measures. Alcohol-based antiseptics for hand hygiene are an appealing innovation because of their efficacy in reducing hand contamination and their ease of use, especially when sinks and supplies for hand washing are limited. Creation of a 'step-down' neonatal care unit for very-low-birth-weight babies with mothers providing primary care has been shown to lead to early discharge and reduction in hospital-acquired infection rates in Pakistan. These interventions can be delivered through facility-based services, population outreach, and also family/community strategies.

Table 7 Major reasons for the nosocomial spread of sepsis and meningitis in a neonate

Lack of aseptic technique for procedures
Inadequate hand hygiene and glove use
Lack of essential equipment and supplies
Failures in sterilization/disinfection or handling/storage of multi-user equipments, instruments, equipment and supplies, leading to contamination
Inadequate environmental cleaning and disinfection
Overuse of invasive devices
Re-use of disposable supplies without safe disinfection/ sterilization procedures
Pooling or multiple use of single-use vials
Overcrowded and understaffed labor and delivery rooms
Excessive vaginal examinations
Failures in isolation procedures/inadequate isolation facilities for babies infected with antibiotic-resistant or highly transmissible pathogens
Unhygienic bathing and skin care
Lack of early and exclusive breast feeding
Contaminated bottle feedings
Absence of mother–baby cohorting
Lack of knowledge, training, and competency regarding infection control practice
Inappropriate and prolonged use of antibiotics

The role of breast feeding

Early initiation of breast feeding improves neonatal health outcomes through several mechanisms. Mothers who suckle their offspring shortly after birth have a greater chance of successful breast feeding throughout infancy. Breast milk provides a variety of immune and nonimmune components that accelerate intestinal maturation, resistance to infection, and epithelial recovery from infection. Prelacteal feeding with nonhuman milk antigens may disrupt normal physiologic gut priming.

Application of antiseptics to the umbilical cord and skin care

Although WHO currently recommends dry cord care for newborns, the application of antiseptics such as chlorhexidine has been shown to kill bacteria, and in community studies, to reduce rates of newborn cord infection and sepsis. Somewhat related is the issue of general skin care. A randomized controlled trial of topical application of sunflower seed oil to preterm infants in an Egyptian neonatal intensive care unit (NICU) showed that treated infants had substantially improved skin condition and half the risk of late-onset infection.

Maternal preventive strategies

For prevention of tetanus, at least two doses of inactivated tetanus toxoid vaccine should be given during pregnancy, so that protective antibodies can be transferred to the fetus before birth and protect it from neonatal tetanus. Women with a history of prolonged rupture of membranes, especially if preterm (PPROM), should be given antibiotics prophylactically. Maternal antibiotic therapy in this situation is effective in prolonging pregnancy and in reducing maternal and neonatal infection-related morbidities. Babies born to women with PPROM who received erythromycin, in a multicountry study (ORACLE I) from urban centers, had significant health benefits. Birth attendants can potentially be trained to recognize PPROM, provide referral, and, possibly, provide initial antimicrobial therapy.

Group B streptococcal (GBS) infections are an important cause of neonatal infections in developed countries. Guidelines developed and implemented in the United States have led to a significant reduction in the burden of disease. The majority of newborns born to mothers with risk of GBS colonization undergo a full diagnostic evaluation and empiric therapy.

Medical Treatment

Promptly reaching, identifying, and treating sick newborn infants with infections is critical to their survival. Case management of neonatal infections is mainly provided through child health services, both in facilities and through family/community care. Guidelines for integrated management of pregnancy and childbirth (IMPAC) identify opportunities for combining, and scaling up, maternal and neonatal care. Similarly, integrated management of childhood illness (IMCI) has been widely implemented as the main approach for addressing child health in health systems. However, IMCI management guidelines do not as yet include the first week of life, which is the highest risk period for child mortality. IMCI also depends on the sick child being brought to a health facility. Modifications of IMCI to include the neonatal period (IMNCI) and expansion to community settings have now been included as a public health strategy in many countries, including India. The ideal strategy would be to provide linked community setting care with referral to facilities in case of need.

Recent studies have demonstrated significant reductions in neonatal mortality with the use of oral co-trimoxazole and injectable gentamicin by community health workers. This strategy could be employed in circumstances where referral is difficult. Currently, in some health systems outreach health workers and community nutrition and child development workers are being trained to visit all mothers and neonates at home two to three times within the first 10 days of life, to provide home-based preventive care/health promotion and to detect neonates with sickness requiring referral. Extra contacts are proposed for LBW babies. With slight modifications, these visits can be used to provide postpartum care to the mother as well.

A combination of ampicillin and gentamicin is often used to treat neonatal sepsis in health-care facilities. However, increasing antibiotic resistance among common neonatal pathogens, in both community and hospital settings, is making appropriate antibiotic choice difficult, and guidelines for the treatment of neonatal sepsis are in flux. Furthermore, local antibiotic resistance patterns may differ substantially. This issue is discussed at greater length in the section on treatment of childhood meningitis. Table 8 shows the antibiotic treatment of sepsis and meningitis in neonates.

Childhood Meningitis

Meningitis is a potentially fatal infection. It is also associated with the risk of chronic morbidity and developmental disability.

Global and Regional Epidemiology

Although the exact incidence of meningitis in developing countries is uncertain, CFRs are estimated to range from 10 to 30%. Furthermore, despite treatment between 20% and 50% of survivors develop neurological sequelae. There is a relative paucity of microbiological information from developing countries, but beyond the neonatal period, the main agents of meningitis include *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae,* and *Nisseria meningitidis* with reported CFRs of 7.7%, 10%, and 3.5%, respectively. Table 9 shows the common bacteria causing meningitis in the developing and developed countries.

Issues in Presentation and Diagnosis

The clinical features that may help in diagnosing meningitis are summarized in Table 10. In general, a low threshold is kept for investigating and excluding meningitis in children as features may be nonspecific. The clinical diagnosis can be confirmed by lumbar puncture and the examination of CSF. The CSF will have a cloudy appearance and the presence of pathogens on Gram stain, or as indicated by latex agglutination, is the definitive method of diagnosis.

Preventive Measures

Although poverty, malnutrition, and overcrowding are important risk factors for meningitis, delayed and inappropriate case management is a common determinant of adverse outcomes. The development of effective vaccines has substantially reduced the burden of meningitis in the developed world. These vaccines include Hib, pneumococcal, and *N. meningititis.*

Haemophilus influenzae *type b (Hib) vaccine*

Currently three Hib conjugate vaccines are available for use in infants and young children with comparable efficacy rates of greater than 90% protection against invasive disease. All industrialized countries now include Hib vaccine in their national immunization programs, which has resulted in the virtual elimination of invasive Hib disease in these richer countries. There is comparable impressive evidence of benefit from several developing countries following introduction of Hib vaccine, and many countries are beginning to include Hib vaccine in their repertoire with support from the Global Alliance for Vaccines and Immunization.

Pneumococcal vaccine

The recent development of 7-valent protein-conjugate polysaccharide vaccine (7-PCV), 9-valent, and 11-valent vaccines is a major advance in the control of invasive pneumococcal disease, as the older 23-valent polysaccharide vaccine (23-PSV) is unsuitable for young children. In the United States, the 7-PCV was included in routine vaccinations of infants and children under 2 years in

Table 8 Antibiotic treatment of neonatal meningitis and sepsis

		Antimicrobial choice	
Patient group	*Likely etiology*	*Developed countries*	*Developing countries*
Sepsis			
Immunocompetent children	Developed countries: *Streptococcus* (Group B) *E. coli* Developing countries: *Klebsiella* *Pseudomonas* *Salmonella*	Ampicillin/Penicillin plus gentamicin	Ampicillin/Penicillin plus aminoglycoside Or Co-trimoxazole plus gentamicin
Meningitis			
Immunocompetent children (age < 3 months)	Developed countries: *Streptococcus* (Group B) *E. coli* *L. monocytogenes* Developing countries: *S. pneumoniae* *E. coli*	Ampicillin plus ceftriaxone or cefotaxime	Ampicillin plus gentamicin
Immunodeficient	Gram-negative organisms: *L. monocytogenes*	Ampicillin plus ceftazidime	

Table 9 Comparison of bacterial meningitis etiology in the developing and developed world (prior to the widespread introduction of Hib vaccine)

	Developing countries	*Developed countries*
H. influenzae	30%	65%
S. pneumoniae	23%	13%
N. meningitidis	28%	18%
Other organisms	19%	4%

Table 10 Signs and symptoms of childhood meningitis

Symptoms	*Signs*
Vomiting	Stiff neck
Inability to feed and drink	Repeated convulsions
Headache or pain in back of neck	Fontanelle bulging
Convulsions	Petechia/purpura
Irritability	Irritability
Recent head injury	Lethargy
	Evidence of head trauma
Signs of raised intracranial pressure additional	
Unequal pupils	
Rigid posture or posturing	
Focal paralysis in any limbs or trunk	
Irregular breathing	

2000, and by 2001 the incidence of all invasive pneumococcal disease in this age group had declined by 69%. Currently several Latin American countries are beginning to introduce PCV as part of their Expanded Program for Immunization (EPI) programs.

N. meningitidis *('Meningococca') vaccine*

A polysaccharide vaccine is available for A, C, W-135, and Y strains of *N. meningitides*. It is being introduced in several developed countries as part of routine vaccine schedules, especially for those adolescents who will be rooming in crowded college dormitories.

Medical Treatment

The mainstay of treatment is prompt antibiotic therapy for suspected bacterial meningitis, which needs to be started before the results of CSF culture and sensitivity are available. This requires selection of an appropriate antibiotic, known to be effective against the common bacterial pathogens prevalent locally. An increasing number of β-lactamase-producing strains of Hib are resistant to ampicillin (a β-lactamase is an enzyme that destroys penicillin class antibiotics, such as ampicillin). A smaller number of chloramphenicol acetyltransferase-producing strains are resistant to chloramphenicol. Additionally, the proportion of CSF isolates of *S. pneumoniae* that are resistant to penicillin, ceftriaxone, and cefotaxime has also increased. Currently, the drugs for either suspected or confirmed bacterial meningitis include cefotaxime (or ceftriaxone) alone or with ampicillin (preferred). If this is not available, then ampicillin plus either gentamicin or chloramphenicol may be used. If sepsis is suspected, then cases should be treated with ampicillin or penicillin plus an aminoglycoside, until meningitis is confirmed. Antimicrobial therapy is described further in Table 11.

Ancillary therapy

Very early parenteral administration of corticosteroids (before or with initiation of antibiotics) significantly

reduces severe adverse outcomes and CFRs. Although a meta-analysis of randomized, controlled trials has shown the benefit of steroids in all-cause bacterial meningitis, predominantly Hib meningitis, a recent study of their use in pneumococcal meningitis found no significant benefits. However, there was a significantly lower rate of hearing loss in the treatment group at 3 months post-discharge. Similarly, there is evidence to suggest that restriction of fluids in the first 48 hours may improve outcomes.

Pneumonia

Acute respiratory infections (ARIs) are classified as upper, or lower, respiratory tract infections and include laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, and any combination thereof. ARIs are the most common causes of both illness and mortality in children under 5 years with bronchiolitis and pneumonia accounting for the maximum number of deaths. ARIs not only are confined to the respiratory tract, but also have systemic effects because of possible extension of infection or microbial toxins, inflammation, and reduced lung function.

Global and Regional Epidemiology

The annual childhood ARI incidence in Europe and North America is 34 to 40 cases per 1000, higher than at any other time of life, except perhaps in adults older than 75 or 80 years of age. Pneumonia is the most severe and largest killer of children, causing almost 20% of all child deaths globally. Recent estimates indicate that there are approximately 1.9 million pneumonia deaths annually (95% confidence interval, 1.6–2.2 million); with 75% of all childhood pneumonia cases occurring in just 15 countries. **Table 12** shows the pathogen-specific causes of childhood pneumonia.

Issues in Presentation and Diagnosis

Currently, the standard WHO algorithm for ARI detection by community workers defines nonsevere pneumonia as cough or difficult and fast breathing (respiratory rate of 50 breaths per minute or more for children aged 2 months to 11 months; or respiratory rate of 40 breaths per minute or more for children aged 12 months to 59 months), and either documented fever of above 101 °F or chest in-drawing. Elsewhere, severe pneumonia has been defined as having cough or difficult breathing, with tachypnea and in-drawing of the lower chest wall (with or without fast breathing); and very severe pneumonia/disease, cough or difficult breathing with one or more danger signs (central cyanosis, inability to drink, or unusually sleepy).

The WHO has defined pneumonia solely on the basis of clinical findings obtained by visual inspection and by setting respiratory rate cutoffs. It is recognized that mortality in children due to ARI could be reduced by one half if early detection and appropriate treatment are provided.

Evidence-Based Interventions

Only in the early 1980s, long after immunization and diarrhea control programs were launched, did the international community become aware of the epidemiological magnitude of ARI and the need for action. The WHO and UNICEF decided that the reduction of pneumonia mortality would be the main initial ARI program objective. Only about half of children with pneumonia receive appropriate medical care, and, according to limited data from the early 1990s, less than 20% of them receive antibiotics. Microbiological studies in hospitalized children with pneumonia in developing countries have shown that bacteria are present in more than 50% of all cases, with an increasing proportion of bacterial cases in more severe cases. Thus, prompt treatment with a full course of effective antibiotics can be life-saving. Measles associated pneumonia is an important cause of death particularly in malnourished children, with mortality rates as high as 50% in some studies.

Preventive Measures

Poverty, overcrowding, air pollution, malnutrition, harmful traditional practices, and delayed and inappropriate

Table 11 Treatment of childhood meningitis

Patient group	*Common organisms*	*Antimicrobial treatment*
Immunocompetent children (aged $\geq$ 3 months – 18 yrs)	*H. influenzae* *S. pneumoniae* *N. meningitidis*	Developing countries: Ampicillin plus chloramphenicol Developed countries: Cefotaxime or ceftriaxone[a]
Immunodeficient	*L. monocytogenes*	Ampicillin plus ceftazidime
Neurosurgical problems and head trauma	*S. aureus* *S. pneumoniae*	Vancomycin plus 3rd generation cephalosporin

[a]For resistant *S. pneumoniae,* the American Academy of Pediatrics recommends vancomycin plus cefotaxime or ceftriaxonease empiric therapy.

Table 12 The pathogen-specific causes of childhood pneumonia

Age range	*Most common causative organism*
Neonates (from birth to 30 days after birth)	*Streptococcus pyogenes*, *Staphylococcus aureus*, *Escherichia coli*
Infants (from 3 wks to 4 mos)	*Streptococcus pneumoniae*
Infants older than 4 mos and in preschool-aged children	Viruses and *Streptococcus pneumoniae*
Children in developing countries	*Staphylococcus aureus* and *Haemophilus influenzae*, including nontypeable

case management are important underlying determinants for high ARI case-fatality rates. Preventive strategies for pneumonia include the reduction of the incidence of LBW, ensuring warmth after birth and appropriate feeding, immunizing children, promoting adequate nutrition (including exclusive breast feeding and zinc intake), and reducing indoor air pollution. Vitamin A has been found to substantially reduce mortality from measles.

The use of vaccines

Three vaccines have the potential to substantially reduce ARI deaths in children under 5 years of age, that is, the Hib, measles, and pneumococcal vaccines. As discussed earlier, several versions of both the Hib and pneumococcal vaccines exist and have been shown to be efficacious. Newer improved versions of PCV may be available by 2010 and have the potential to significantly reduce pneumonia deaths in developing countries.

The effect of hand washing

Many respiratory pathogens are spread as fomites or by hand-to-hand contact, and not as aerosols. Thus, basic hygiene measures such as hand washing can be effective tools for preventing ARI. Controlled trials of hand washing promotion in child-care centers in developed countries have reported significant reduction (12–32%) in rates of upper respiratory tract infections. A community-based cluster randomized trial of hand washing promotion from Pakistan also reported that frequent hand-washing (with or without soap) led to a 50% reduction in pneumonia incidence and a 36% lower incidence of impetigo.

The effect of reduction in indoor air pollution

About 3 billion people still rely on solid fuels for cooking and heat. Approximately 2.4 billion people use biomass fuels such as wood or dried cow dung, and the rest rely on coal, mostly in China. Globally there is marked regional variation in solid fuel use with rates of less than 20% in Europe and Central Asia and greater than 80% in Sub-Saharan Africa and South Asia, intricately linking to poverty. More than half of all the deaths and 83% of disability-adjusted life years (DALYs) lost attributable to solid fuel use occur as a result of lower respiratory tract infection (pneumonia) in children under 5 years of age. A systematic review of the health outcomes resulting from indoor air pollution, including pneumonia, indicated that substantial pneumonia prevention benefits could occur from mitigating indoor air pollution.

The role of zinc in prevention

Previously, a meta-analysis of trials of daily preventive zinc supplementation showed a significant impact on pneumonia incidence. A recent update of this meta-analysis reaffirms the impact on reduction in the risk of respiratory tract infections (by 8%) but not on duration of disease.

Medical Treatment

Antibiotic treatment of pneumonia

Although recommendations for antibiotic therapy for pneumonia are often based on identification of the causative organism, in routine clinical care this is rare and difficult, and empirical antibiotic therapy is instituted. Since *S. pneumoniae* and *H. influenzae* are the most common causes of childhood pneumonia in developing countries, the WHO recommends using oral cotrimoxazole or amoxicillin as first-line drugs for the treatment of nonsevere pneumonia at first-level health facilities. Cloxacillin or other antistaphylococcal antibiotics should be available to treat cases in which the initial combination fails within 48 hours. Young infants with signs of pneumonia, sepsis, or meningitis should be referred to a hospital for parenteral rather than oral treatment. Similarly, children with pneumonia and malnutrition should be referred to a hospital for tuberculosis evaluation as well as for parenteral antimicrobial treatment for bacterial pneumonia.

The various modalities for antibiotic treatment according to disease severity are shown in **Table 13**. However, resistance to first-line antimicrobial drugs recommended for home treatment of nonsevere pneumonia has led to treatment failure rates as high as 22%. Recent data on standard antimicrobial treatment of severe pneumonia in HIV-infected children in Africa with parenteral penicillin or amoxicillin show failure rates of 24%, which is even more alarming.

Antibiotic treatment of pneumonia in HIV-infected children

The current WHO ARI treatment guidelines were designed before the rise of HIV infection in sub-Saharan Africa, and they do not include empiric treatment for *Pneumocystis (carinii) jiroveci* infection. Daily administration of cotrimoxazole (trimethoprim-sulfamethoxazole) is

advocated since it reduces deaths from opportunistic infections in symptomatic HIV-infected children, including pneumonia caused by *Pneumocystis*. It has been shown that standard empiric therapy for severe pneumonia with injectable penicillin or oral amoxicillin in infants is inadequate where HIV prevalence is high. The benefits of the WHO ARI guidelines would be enhanced if they could be modified for areas with high rates of HIV infection and where the pneumonia burden is high, even in HIV-negative children.

Integrated management of childhood infections (IMCI)

In the mid-1980s, WHO initiated a control program for ARI that focused on cases managed by health workers. The WHO current case management of ARI has been incorporated into the global IMCI which trains health workers to recognize fast breathing, lower chest wall in-drawing, or danger signs in children with respiratory symptoms (such as cyanosis or inability to drink). One criticism of this approach is that there may be other conditions that mimic pneumonia, which may result in inappropriate antibiotic therapy, thereby contributing to antibiotic resistance. On balance, however, the need to provide treatment to children with pneumonia may outweigh these concerns.

Implications for Public Health

Despite the introduction of a global program for ARI control almost 15 years ago, there has been little change in the overall burden of pneumonia deaths. The bulk of deaths from childhood pneumonia disproportionately affect the poor who have many risk factors for developing ARI, such as overcrowding, poor environmental conditions, and malnutrition, as well as limited access to curative and preventive health services. The importance of reaching the poor with pneumonia in community settings must be underscored. Such strategies involve recognizing the disease, ambulatory management of pneumonia in community settings through community health workers, assuring transportation and access to facilities for severe pneumonia, and availability of antibiotics. As more vaccines active against pneumonia pathogens become available at costs appropriate for poor countries, their incorporation into community-based strategies should be promoted.

Diarrhea

Infectious diarrhea remains a principal cause of preventable morbidity and mortality among developing world children under 5 years.

Global and Regional Epidemiology

Several recent reviews have evaluated diarrhea burden and mortality rates. Snyder *et al.* (1982) estimated that 4.6 million children died annually from diarrhea two decades ago. Kosek *et al.* (2003) have recently updated these estimates by reviewing 60 studies of diarrhea morbidity and mortality published between 1990 and 2000. They conclude that diarrhea accounts for 21% of all deaths at under 5 years of age and causes 2.5 million deaths per year, although morbidity rates remain relatively unchanged. Despite the different methods and sources of information, each successive review of the diarrhea burden over the past 3 decades has demonstrated declining mortality but relatively stable morbidity. Persistent high rates of diarrhea morbidity may have significant long-term effects on linear growth and physical and

Table 13 Treatment of pneumonia according to disease severity

Signs/symptoms	*Classification*	*Treatment*
Fast breathing: ≥60 breaths/min in child aged < 2 mos ≥50 breaths/min in child aged 2–11 mos ≥40 breaths/min in child aged 1–5 yrs Definite crackles on auscultations	Pneumonia	Home care Give appropriate antibiotics for 5 days Soothe the throat and relieve the cough with a safe remedy Advise the mother when to return immediately Follow-up in 2 days
The signs of pneumonia plus chest wall in-drawing	Severe pneumonia	Admit to hospital Give the recommended antibiotics Manage airway Treat high fever if present
The signs of severe pneumonia plus central cyanosis, severe respiratory distress, and inability to drink	Very severe pneumonia	Admit to hospital Give the recommended antibiotics Give oxygen Manage airway Treat high fever if present

cognitive function in children. Figure 4 shows specific trends for diarrhea in the world from 1954 to 2000.

Issues in Presentation and Diagnosis

Overall, three major diarrhea syndromes are recognized. These are acute watery diarrhea, bloody (invasive) diarrhea, and persistent diarrhea.

Acute watery diarrhea

Acute watery diarrhea can be rapidly dehydrating, with stool losses of 250 ml/kg/day or more, a quantity that quickly exceeds total plasma and interstitial fluid volumes and is incompatible with life unless fluid therapy can keep up with losses. Such dramatic dehydration is usually due to rotavirus, enterotoxigenic *E. coli*, or *V. cholerae*, and it is most dangerous in the very young.

Bloody (invasive) diarrhea

Bloody diarrhea is a manifestation of invasive intestinal infection and is associated with intestinal damage and nutritional deterioration, often with systemic manifestations including fever. It accounts for approximately 10% of diarrheal episodes, and approximately 15% of diarrheal deaths, in children under 5 years of age worldwide. Although clinicians often use the term interchangeably with dysentery, the latter is a specific syndrome consisting of the frequent passage of characteristic, small-volume, bloody mucoid stools; abdominal cramps; and tenesmus. Although less frequent than acute diarrhea, bloody diarrhea generally lasts longer, is associated with a higher rate of complications and case fatality, and is more likely to adversely affect a child's growth. Agents such as *Shigella* or specific *E. coli* that cause bloody diarrhea or dysentery can also provoke a form of diarrhea that clinically is not bloody diarrhea, although mucosal damage and inflammation are present and fecal blood and white blood cells are usually detectable by microscopy.

Persistent diarrhea

Persistent diarrhea is defined as diarrhea (either watery or bloody) lasting 14 days or longer, manifested by malabsorption, nutrient losses, and wasting; and is typically associated with malnutrition. Although persistent diarrhea accounts for 8 to 20% of the total number of diarrhea episodes, it is associated with a disproportionately increased risk of death. Persistent diarrhea more commonly follows an episode of bloody diarrhea with a 10-fold higher risk of mortality. HIV infection is another risk factor for persistent diarrhea in both adults and children.

Evidence-Based Intervention

Use of oral rehydration solution (ORS), improved nutrition, increased breast feeding, better supplemental feeding, female education, measles immunization, and sanitation and hygiene improvements have contributed to substantial declines in the morbidity and mortality of diarrhea over the past 30 years. Syndromic diagnosis provides important clues to optimal management and is both programmatically and epidemiologically relevant. The best outcome for diarrhea requires that mothers recognize the problem and seek medical care promptly; and that health workers give ORS or other fluids to prevent or treat dehydration, dispense an appropriate antibiotic when needed, advise on appropriate feeding, and provide follow-up, especially for children at increased risk of

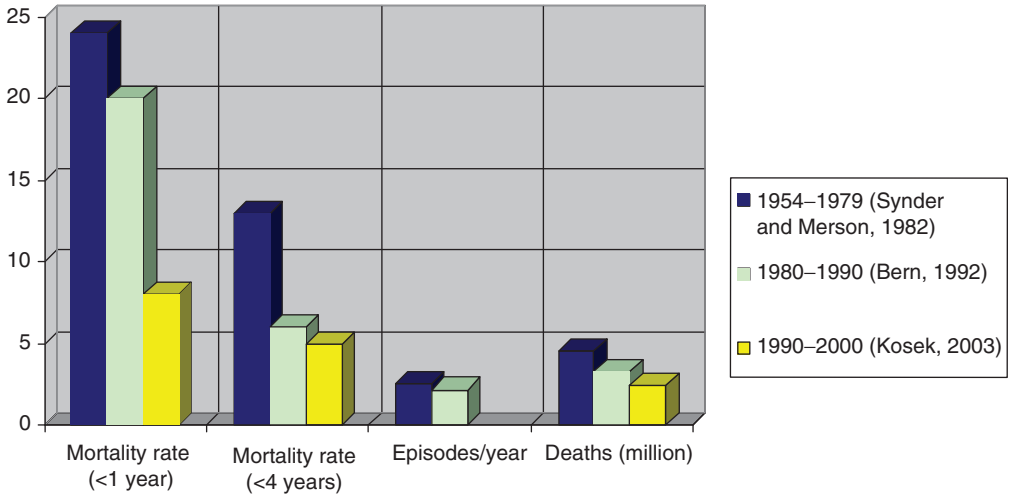

Figure 4 Diarrhea-specific trends from three reviews of active surveillance in the developing areas from 1954 to 2000. Reproduced with permission from Kosek M, Bern C, Guerrant RL (2003) The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bulletin of the World Health Organization* 81: 197–204.

serious morbidity or death. Recently, low osmolality ORS and zinc supplementation (10–20 mg/day) have led to significantly improved diarrhea outcomes.

Preventive Measures

Malnutrition is an independent predictor of frequency and severity of diarrheal illness and can lead to a vicious cycle in which sequential diarrheal episodes to increasing nutritional deterioration, impaired immune function, and greater susceptibility to infection.

Although diarrheal disease can affect anyone, a strong relationship exists between poverty, an unhygienic environment, access to adequate and affordable health care, the ability to provide appropriate diets, and the number and severity of diarrheal episodes – especially for children under 5 years of age. Thus, preventive and management strategies for diarrhea must have an equity focus.

Family knowledge about diarrhea must be reinforced in areas such as prevention, nutrition, hand washing and hygiene, measles vaccination, preventive zinc supplements, and when and where to seek care. It is estimated that in the 1990s, more than 1 million deaths related to diarrhea might have been prevented each year, had these interventions been implemented at scale.

The role of breast feeding

A meta-analysis of three observational studies in developing countries shows that breast-fed children under age 6 months are 6.1 times less likely to die of diarrhea than infants who are not breast-fed. Continued breast feeding during the diarrhea episode provides nutrients to the child, prevents weight loss, and improves recovery from diarrhea.

Improved and safe complementary feeding

Contaminated and poor-quality complementary foods are associated with increased diarrhea burden and stunting. Ideally, complementary foods should be introduced at age 6 months, and breast feeding should continue for up to 2 years or even longer. Appropriate, safe, and aptly initiated complementary feeding has been shown to significantly reduce mortality in young children. Recent data from preventive use of probiotics suggest that these may have promise for the prevention of diarrhea episodes.

Diarrhea frequently causes fever, altering host metabolism and leading to the breakdown of body stores of nutrients. Those losses must be replenished during convalescence, which takes much longer than the illness does to develop. For these reasons, appropriate feeding strategies during diarrhea episodes are a cornerstone of treatment. Available evidence indicates that while special formulas are widely used, in most developing countries dietary management of diarrhea is possible with home-available diets.

The role of zinc in the prevention of diarrhea

Various studies suggest that zinc-deficient populations are at increased risk of developing diarrheal diseases, respiratory tract infections, and growth retardation. A meta-analysis published in 1999 showed that continuous zinc supplementation was associated with decreased rates of childhood diarrhea, and a recent meta-analysis confirms the previous findings and indicates that zinc supplementation for young children leads to reduction in the risk of diarrhea (by 14%), serious forms of diarrhea, and the number of days of diarrhea per child.

Improved water and sanitary facilities and promotion of personal and domestic hygiene

Human feces and contamination are the primary source of diarrheal pathogens. Poor sanitation, lack of access to clean water, and inadequate personal hygiene are responsible for an estimated 90% of childhood diarrhea. Promotion of hand washing reduces diarrhea incidence by an average of 33%, and rigorous observational studies have demonstrated a median reduction of 55% in all-cause child mortality associated with improved access to sanitation facilities. Hand-washing promotion strategies have been shown to reduce diarrhea burden with ancillary benefits in community settings.

The role of measles vaccine

Measles is known to predispose to diarrheal disease secondary to measles-induced immunodeficiency. It is estimated that measles vaccine at varying levels of coverage (45–90%) could prevent 44 to 64% of measles cases, 0.6 to 3.8% of diarrheal episodes, and 6 to 26% of diarrheal deaths among children under 5 years of age. Global measles immunization coverage is now approaching 80%. The disease has been eliminated from the Americas, raising hopes for global elimination in the near future, with a predictable reduction in diarrhea as well.

Medical Treatment

Oral rehydration therapy (ORT)

ORS, ORT, and other components of clinical management of diarrhea have made a significant contribution to reducing deaths from diarrhea. For more than 25 years, UNICEF and WHO have recommended a single formulation of glucose-based ORS considered optimal for cholera, irrespective of cause or age group affected. However, in comparison with standard ORS, low-osmolality ORS with lower sodium and glucose concentration further reduces stool output, vomiting, and the need for intravenous fluids. Full details of the management of diarrhea and dehydration are beyond the scope of this article; however, **Figure 5** summarizes various steps in diarrhea management.

In home settings, dehydration can usually be prevented by having the child drink recommended home fluids or by providing food-based fluids (such as gruel, soup, or rice-water) as soon as the diarrhea starts. If dehydration occurs, the child should be brought to a community health worker or health center for further treatment. Where feasible, families should have ORS ready-to-mix packages and zinc (syrup or tablet), readily available for use. Breast feeding should continue simultaneously with the administration of appropriate fluids or ORS.

Ancillary therapy

Given that *Shigella* spp. cause about 60% of dysentery cases and nearly all episodes of life-threatening dysentery, appropriate treatment of invasive diarrhea must include oral antibiotics as dictated by local susceptibility patterns. Oral zinc supplements (10–20 mg elemental zinc/day for 10–14 days) should be given to children with acute diarrhea. Recent studies do not reveal any added benefit of administering zinc for infants under 6 months of age with diarrhea.

Adsorbents (such as kaolin, pectin, or activated charcoal) are not useful for treatment of acute diarrhea. Antimotility drugs (such as tincture of opium or loperamide) may be harmful, especially in children under 5 years of age, although they decrease diarrheal flux.

Malaria

Global and Regional Epidemiology

Malaria is the most important of the parasitic human diseases, with 107 countries and territories (with half the human population) at risk of transmission. Although people of all ages can be victims of this infectious disease, children and pregnant women suffer the most. Recent estimates of the global falciparum malaria morbidity burden have increased the number to 515 million cases, with Africa suffering the vast majority of this toll. Of the four species affecting humans, *Plasmodium falciparum* (the most lethal species) and *P. vivax* (like *P. falciparum,* quite widespread) are more important than *P. ovale* or *malariae.* Almost 250 million clinical episodes of malaria occur among children in endemic areas annually, with an estimated 1 million deaths annually. Severe attacks in children include about 1 million cases of cerebral malaria and 4 million cases of severe anemia. Of children with clinical attacks, several thousand have neurological damage and up to 250 000 will have developmental problems.

Current trends in global climate change suggest that malaria incidence may increase dramatically worldwide. Furthermore, efforts to create more impounded water reservoirs to meet drinking water MDG objectives will inevitably increase vector breeding opportunities.

Issues in Clinical Presentation and Diagnosis

Normally people with malaria develop an abrupt onset of fever (a 'fever spike'), accompanied with chills; other symptoms include headache, musculo-skeletal discomfort, periods of high fever separated by normal temperature, nausea, vomiting, abdominal pain, splenomegaly, and, less commonly, hepatomegaly. Fever spikes followed by sweating are a prominent feature. Anemia is common, and is associated with 17 to 54% of malaria-attributed deaths in children under 5 years of age.

Malaria is often more common during the rainy season or afterward, as stagnant water reservoirs provide

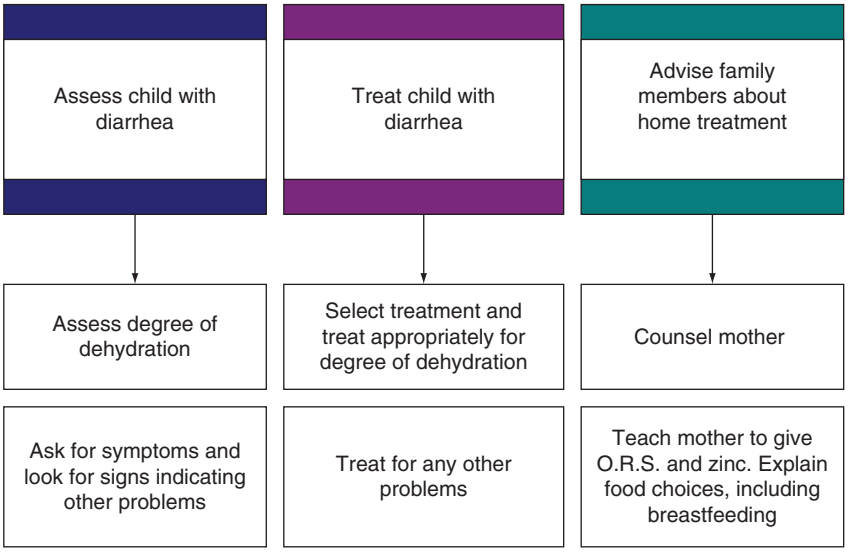

Figure 5 The steps to treat diarrhea. Source: World Health Organization, Integrated Management of Childhood Illness. http://www.who.int/child_adolescent_health/topics/prevention_care/child/imci/en/

breeding sites for the *Anopheles* mosquito vectors. Malaria due to *P. vivax* is an acute illness, in a nonimmune patient, having recurrent and paroxysmal fever 'spikes' associated with chills and drenching sweats. Falciparum malaria is associated with mortality rates of up to 40% in naive hosts, as well as the bulk of severe disease (such as cerebral malaria, severe anemia, and the dreaded though rare blackwater fever), while the other species may result in fatality rates of 1 to 2%.

The gold standard for malaria diagnosis is parasite detection in blood smear or via antigen-based rapid diagnostic tests. If laboratory diagnosis is not feasible or is difficult, then the diagnosis is made on clinical grounds. Health workers must monitor the therapeutic efficacy of drugs closely and have on hand different treatment policies when parasite resistance to chloroquine, sulfadoxine-pyrimethamine (SP), and other drugs emerges. Artemesinin-based regimens, despite their high costs, are now required in many parts of the world. Concerns include unreliable and inaccurate microscopy and the disadvantages of alternative tests, plus the widespread distribution and use of substandard and counterfeit drugs.

Maternal or fetal malaria infection during pregnancy can be fatal, or may lead to stillbirths, low birth weight births, spontaneous abortion, and maternal anemia. Other long-term effects of malaria include anemia and impaired cognitive development after cerebral malaria, a condition characterized by diffusely impaired cerebral blood flow.

Preventive Measures

Preventive measures against malaria require public–private cooperation. They include netting of the windows and other open channels, and environmental management of stagnant water to remove mosquito breeding sites. To kill developing mosquito larvae, breeding sites should be drained, larvae-eating fish can be introduced, and organic oils such as kerosene can be spilled onto stagnant water reservoirs. Recent and historical evidence suggests that drinking and irrigation water reservoir management can significantly decrease mosquito population densities.

Insect repellants such as *N,N*-diethyl-3-methylbenzamide (DEET), and pyrethrins are advised in malaria-dominant areas. Although DDT spraying did not lead to malaria eradication in the past, there is growing interest (and controversy) in this as a public health strategy in endemic areas despite its toxic effects in animals, including humans, when it bio-accumulates. Bed nets treated with insecticide can prevent transmission of nocturnally transmitted, vector-borne diseases including malaria. Insecticide-treated bed nets (ITNs), insect-treated curtains, and other insecticide-treated materials (ITMs) are considered highly effective against new malarial cases, and have proven to be valuable preventive measures that can be applied in the highly endemic areas. The use of ITNs has been shown to reduce the incidence of uncomplicated malaria by about 39 to 50%.

Intermittent preventive treatment in infancy (IPTi) refers to full therapeutic doses of an antimalarial at specified time points to cure incipient malaria, usually with single doses of therapeutic agents. It has fewer adverse events than continuous prophylaxis because it is taken less often, and it is easier to deliver through clinics, reducing the poor adherence of self-administration. Although questions remain concerning the safety, sustainability, and public health impact of this intervention for children, the potential gains are large in terms of a possible effect on malaria episodes, anemia, and mortality.

Malnourished infants and children have higher malaria death rates, and reducing malnutrition may reduce malaria mortality. Although a previous meta-analysis of zinc supplementation suggested a reduction in malaria incidence, recent randomized controlled trials do not show much impact. Recent studies of iron supplementation among children in malaria-endemic areas suggest that the risk of malaria hospitalization and mortality increases significantly, perhaps because malaria parasites require iron as a nutrient. Thus, care must be undertaken in isolated nutrient interventions, and, instead, improvement in general nutrition status must be targeted.

Medical Treatment

In endemic areas any febrile illness in infants and children should be suspected and treated as malaria, especially if laboratory confirmation is not available. For sensitive strains of malaria in Central America and the Middle East, chloroquine is the drug of choice. During the past 2 to 3 decades, chloroquine-resistant strains have evolved in Asia, Africa, and Latin America. These require treatment with SP, mefloquine, quinine, or artemisinin combination therapy (ACT). Primaquine can be used to kill dormant hepatic malaria forms that can cause relapses of *P. vivax* and *ovale*.

The preferred treatment for malaria in areas with resistance to single drugs or multi-drug resistance (MDR) is ACT. While ACT is more expensive, it is a cost-effective intervention in areas with widespread drug-resistant malaria. Also complicating malaria treatment is recent, disquieting data showing that many children with positive blood smears may also have coincident bacterial infections, requiring antimicrobial treatment as well. It should be emphasized that optimal malaria treatment is a topic in flux.

Typhoid

Typhoid fever, a systemic disease caused by *Salmonella enterica* serovar Typhi, is an acute illness characterized

by protean and nonspecific symptoms, including fever and gastrointestinal infection. The systemic disease caused by *S.* paratyphi is clinically similar and both typhoid and paratyphoid are collectively labeled as enteric fevers. Infants suffer substantial morbidity from typhoid and, in addition, the emergence of MDR strains has complicated treatment options.

Global and Regional Epidemiology

Typhoid fever is a major cause of illness, with a global incidence of over 21 million cases with an estimated 216 510 deaths in 2000. Approximately 10.8 million cases occur annually in the developing world (the majority in Asia). Typhoid is a disease confined solely to humans, and its existence in a population is *prima facie* evidence of inadequate water treatment and the lack of separation of human feces from food and water (sanitation). Dramatic outbreaks have occurred when drinking water supplies are contaminated by sewage or after lapses in water chlorination. In travelers to endemic regions, the use of contaminated groundwater, consumption of street foods, and poor personal hygiene are common risk factors for infection. In South Asia, recent community-based studies indicate that children under 5 years suffer high infection rates, and a disproportionately large burden of disease. The global CFR of 1% is based on conservative estimates from hospital-based fever studies, and actual mortality figures may be much higher in areas where referral is difficult, MDR organisms are prevalent, and health services dysfunctional. Table 14 shows the regional distribution of crude typhoid incidence rates.

Issues in Presentation and Diagnosis

Various organs are involved in the course of enteric fever, resulting in a wide array of presentations, and there are no clinically distinct signs and symptoms that unequivocally separate it from other diseases. The incubation period ranges from 5 to 14 days. Most children present with fever, headache and abdominal discomfort, diarrhea, sore throat, anorexia, dry cough or myalgia, and constipation. In the later phase of illness, more specific physical signs include hepatomegaly and splenomegaly. Evanescent skin rashes ('rose spots') may be seen in an early stage of the illness in fair-skinned children, and a large proportion of children have a centrally coated tongue.

Most complications – including intestinal perforation and peritonitis, encephalopathy, intestinal hemorrhage, hepatosplenomegaly, vomiting, and diarrhea – are of late onset. The most serious complication, intestinal perforation, occurs in 0.5 to 3% of the patients with typhoid, and because they occur most commonly in areas where optimal medical care is not readily available, it may be associated with CFRs ranging from 4.8 to 30.5%.

Diagnosis of typhoid and paratyphoid fever requires cultures of blood, bone marrow, stools, or urine to detect the pathogens. Laboratory findings commonly include leucopenia, thrombocytopenia, proteinurea, and elevated hepatic transaminases, but these are relatively nonspecific and are inconsistently found. In developing countries, culture facilities are expensive and confined mostly to hospitals, while most typhoid patients are diagnosed clinically and treated in outpatient settings. In other instances serological diagnosis may be made with the Widal test. The latter, though useful, is insufficiently sensitive in endemic areas and hence there is a need for further refinement in serological or molecular diagnosis of the disease using ELISA or PCR-based tests.

Table 14 Regional distribution of crude typhoid incidence rates

Area/region	*Crude incidence*[a]	*Typhoid cases*	*Incidence classification*
Global	178	10 825 487	High
Africa	50	408 837	Medium
Asia	274	10 118 879	High
Europe	3	19 144	Low
Latin America/ Caribbean	53	273 518	Medium
Northern America	<1	453	Low
Oceania	15	4656	Medium

[a]Per 100 000 persons per year.

Evidence-Based Intervention

Typhoid has essentially disappeared, without the need for population-wide vaccination, from countries with good sanitation, water treatment, and the rejection of untreated sewage for food crop fertilization.

Preventive Measures

Sanitation, personal hygiene, and the provision of clean drinking water are the most critical elements in prevention. When cases occur, preventing secondary transmission through investigating household contacts and commercial food handlers as well as contaminated drinking water sources is essential to containing this disease.

Typhoid vaccines

Older, whole-cell, inactivated typhoid vaccines have been withdrawn because of side effects. There are two licensed vaccines for prevention of disease: oral Ty21a (an attenuated strain of *S. typhi* administered orally) and Vi (the purified bacterial polysaccharide vaccine, given

parenterally). These two vaccines have comparable protective efficacy. Although used primarily for travelers, recently the Vi vaccine has been used for school vaccination programs in large public health settings in Asia. For younger children and infants, the Vi-conjugate vaccine was shown in a series of studies in Vietnam to provide a high degree of protection. However, the vaccine as yet has not been widely produced and administered for public health use.

Medical Treatment

In the pre-antibiotic era, typhoid fever CFRs approached 20%. Treatment with effective antimicrobial agents – such as ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole (cotrimoxazole), and, later, ciprofloxacin – progressively reduced fatality rates to under 1%, except for MDR isolates. Floroquinolones and third-generation cephalosporins are effective in MDR typhoid, but recently *S. typhi* strains with reduced susceptibility to floroquinolones in Asia have emerged, leading to therapeutic failures. Given the considerable morbidity and higher mortality rates reported with MDR typhoid in children, it is imperative that appropriate antibiotic therapy be instituted promptly.

Dengue Fever

In recent years dengue (a mosquito-borne viral disease) has become a major international public health concern. It is the most common and fastest spreading human arboviral disease worldwide. Dengue virus belongs to the family Flaviviridae (single-stranded, nonsegmented RNA viruses) and has four serologically distinct serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Variations in virus strains within and between the four serotypes influence the disease severity with limited protection across serotypes. Secondary infections (particularly with serotype 2) are more likely to result in severe disease and dengue hemorrhagic fever. Humans and mosquitoes are the principal hosts of dengue virus; the mosquito remains infected for life, but the viruses are only known to cause illness in humans and some nonhuman primates. Dengue epidemics occur during the warm, humid, rainy seasons, which favor abundant mosquitoes and shorten the extrinsic (virus multiplication in the mosquito) incubation period.

Global and Regional Epidemiology

More than two fifths of the world's population (2.5 billion) live in areas potentially at risk for dengue. It is endemic in more than 100 countries across the globe, with a distribution pattern similar to that of malaria. South-East Asia and the Western Pacific area are the most seriously affected regions.

In some case series, dengue fever has been reported as the second most frequent cause of hospitalization (after malaria) among travelers returning from the tropics. Global prevalence estimates range from 50 to 100 million annually, including 250 000 to 500 000 cases of dengue hemorrhagic fever, a severe manifestation of dengue, and 25 000 deaths. Around 95% of cases are children under 15 years of age; infants represent 5% of the cases.

Issues in Presentation and Diagnosis

The incubation period can vary from 3 to 14 days (typically 5 to 7 days), and viremia can persist up to 12 days (typically 4 to 5 days). The fever of dengue usually lasts for 5 to 7 days. Fevers persisting beyond 10 to 14 days suggest another diagnosis. The clinical features of dengue vary with patient age. The majority of dengue infections, especially in children, is minimally symptomatic or asymptomatic and may also present with atypical syndromes such as encephalopathy and fulminant liver failure (**Figure 6**).

Classic dengue

Dengue fever is characterized by a high fever of abrupt onset, sometimes with two peaks ('saddle back fevers'), severe myalgias, arthralgia, retro-orbital pain, and headaches. Any of three types of rashes may occur - a petechial rash, a diffuse erythematous rash with isolated patches of normal skin, or a morbilliform rash. There may be hemorrhagic manifestations and leucopenia. Other manifestations include flushed facies, sore throat, cough, cutaneous hyperesthesia, and taste aberrations. Convalescence may be prolonged and complicated by profound fatigue and depression.

Dengue hemorrhagic fever

When only the hemorrhagic manifestation is provoked (by a tourniquet test), the case is categorized as grade I dengue hemorrhagic fever, but a spontaneous hemorrhage, even if mild, indicates grade II illness. Grades III and IV dengue hemorrhagic fever (incipient and frank circulatory failure, respectively) represent dengue shock syndrome with sustained abdominal pain, persistent vomiting, sudden change of fever to hypothermia, alteration of consciousness, and a sudden diminution in platelet count. Around 40% of patients also have liver enlargement and tenderness. Rare presentations of infection include severe hemorrhage, severe hepatitis, rhabdomyolysis, jaundice, parotitis, cardiomyopathy, and variable neurological syndromes. Infection with one serotype is thought to produce lifelong immunity to that serotype but only a few months' immunity to the others. It has also been seen that a person previously infected with a certain serotype will have an

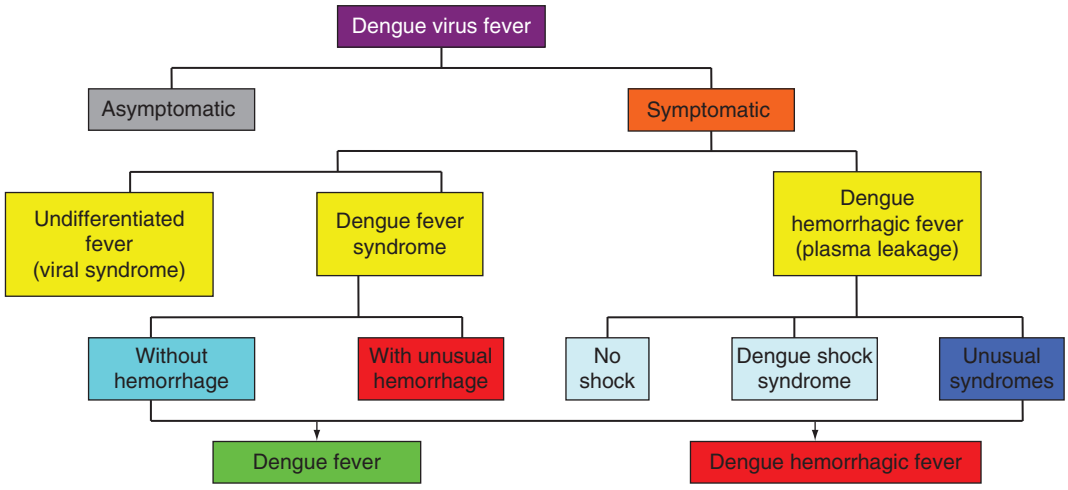

Figure 6 The clinical presentations of dengue virus fever.

increased risk of dengue hemorrhagic fever, compared with those who have not been so infected.

Diagnosis

Differential diagnosis for dengue fever includes typhoid fever, leptospirosis, Epstein-Barr virus, cytomegalovirus, HIV sero-conversion illness, measles, and rubella.

Dengue virus serotypes are distinguishable by complement-fixation and neutralization test. Other tests helpful for the management and diagnosis of patients with dengue include packed cell volume, platelet count, liver function tests, prothrombin time, partial thromboplastin time, electrolytes, and blood gas analysis. Laboratory findings commonly associated with dengue include leucopenia, lymphocytosis, increased serum concentrations of liver enzymes, and thrombocytopenia. Diagnosis can be confirmed with several laboratory tests, most often the hemagglutination inhibition test and IgG or IgM enzyme immunoassays. Platelet counts and hematocrit determinations should be repeated at least every 24 hours to allow prompt recognition of the development of dengue hemorrhagic fever and institution of fluid replacement. Table 15 outlines the clinical categorization of dengue fever.

Evidence-Based Interventions

Rapid urbanization has led to an increase in the environmental factors that contribute to the proliferation of *Aedes* mosquito which transmits dengue. These factors include uncontrolled urbanization, inadequate management of water and waste, and provision of a range of large water stores and disposable, nonbiodegradable containers that become habitats for the larvae. Such environmental factors can change a region from nonendemic (no virus present) to hypoendemic (one serotype present) to hyperendemic (multiple serotypes present).

Preventive Measures

In the absence of a vaccine, environmental control of the vector mosquito, *Aedes aegypti*, is the only effective preventive measure. At a personal level the risk of mosquito bites may be reduced by the use of protective clothing and repellents. The single most effective preventive measure for travelers in areas where dengue is endemic is to avoid mosquito bites by using insect repellents containing DEET. The insect repellents should be used in the early morning and late afternoon, when *Aedes* mosquitoes are most active. These measures require constant reinforcement and may be difficult to sustain because of their cost.

At a public health level, the risk of dengue fever outbreaks can be reduced by removing neighborhood sources of stagnant water or by using larvicides (especially for containers that cannot be eliminated). In addition, predatory crustaceans may be introduced into water bodies.

Vaccines for dengue fever

Live, attenuated tetravalent vaccines are being evaluated in phase 2 trials and have produced 80 to 90% seroconversion rates in trial participants. New approaches to vaccine development now being studied include infectious clone DNA and naked DNA vaccines. These vaccines offer promise in terms of protection against all serotypes as well.

Medical Treatment

No specific therapeutic agents exist for dengue fever apart from analgesia and medications to reduce fever. Treatment is supportive and steroids, antivirals, or carbazochrome (which decreases capillary permeability) have no proven role. However, ribavirin, interferon alpha, and 6-azauridine have shown some antiviral activity *in vitro*. Mild or classic dengue is treated with antipyretic agents

Table 15 Diagnosis of dengue fever and dengue hemorrhagic fever

Dengue fever
Acute illness with two or more of the following:
- Arthralgia
- Headache
- Hemorrhagic manifestations
- Leucopenia
- Myalgia
- Rash
- Retro-orbital pain

WHO definition for dengue hemorrhagic fever
- Evidence of plasma: Leakage caused by increased vascular permeability manifested by at least one of the following:
  - Elevated hematocrit ($\geq$20% over baseline or a similar drop after intravenous fluid replacement)
  - Pleural or other effusion (e.g., ascites)
  - Low protein
- Fever
- Hemorrhagic manifestations
- Platelet count $\leq$ 100 000/mm^3

Dengue shock syndrome
Criteria for dengue hemorrhagic fever:
- Hypotension (defined as systolic pressure $<$ 80 mm/Hg for those aged $<$ 5 yrs or $<$ 90 mm/Hg for those $>$ 5 yrs)
- Pulse pressure $<$ 20 mm/Hg

Probable diagnosis
At least one of the following:
- Occurrence at same location and time as confirmed cases of dengue fever
- Supportive serology

Confirmed diagnosis
At least one of the following:
- Detection of dengue virus or its genomic sequences by reverse transcription
- Fourfold or greater increase in serum IgG or increase in IgM antibody
- Isolation of dengue virus

World Health Organization (WHO) (2006) Working together for health. *World Health Report*. Geneva: WHO.

such as acetaminophen, bed rest, and fluid replacement (usually administered orally and only rarely parenterally). Most cases can be managed on an outpatient basis.

The management of dengue hemorrhagic fever and the dengue shock syndrome is purely supportive with a prominent role for hydration. Aspirin and other nonsteroidal anti-inflammatory drugs should be avoided owing to the increased risk for Reye's syndrome and hemorrhage.

Soil Helminth Infections

Parasitic worms may be the commonest cause of chronic infection in humans. There are about 20 major helminth infections of humans, and all have some public health significance, but the most common are the geo-helminths. In many low-income countries it is more common to be infected than not. Indeed, a child growing up in an endemic community can be infected soon after weaning, and continue to be infected and constantly reinfected for life.

Table 16 Global and regional estimates for helminths

Helminth infections	*Total cases*	*Regions with highest distribution*
Roundworm *(Ascaris lumbricoides)*	807 million	Sub-Saharan Africa, India, China, East Asia
Whipworm *(Trichuris trichiura)*	604 million	Sub-Saharan Africa, India, China, East Asia
Hookworm *(Necator americanus* or *Ancylostoma duodenale)*	576 million	Sub-Saharan Africa, Americas, China, East Asia
Geo-Helminths	$\geq$ 2 billion	

Source: Hotez PJ, Brindley PJ, Bethany JM, King CH, Pearce EJ, and Jacobson J (2008) Helminth infections: the great neglected tropical diseases. *Journal of Clinical Investigation* 118: 1311–1321.

Global and Regional Epidemiology

Recent global estimates indicate that more than a quarter of the world's population is infected with one or more helminths. In low- and middle-income countries, about 1.2 billion people are infected with roundworm (*Ascaris lumbricoides*), and more than 700 million are infected with hookworm (*Necator americanus* or *Ancylostoma duodenale*) or whipworm (*Trichuris trichiura*). In 2002, WHO estimated that 27 000 people die annually from geo-helminthic infections. Many investigators, however, believe that this figure is underestimated. It has been estimated that 155 000 deaths annually occur from these infections (CFR 0.08%). See **Table 16** for the global and regional estimates for helminths.

Health Effects

Children of school age are at greatest risk from the clinical manifestations of disease. Studies have shown associations between helminth infection and undernutrition, iron deficiency anemia, stunted growth, poor school attendance, and poor performance in cognition tests. Some 44 million pregnancies are currently complicated by maternal hookworm infection, placing both mothers and children at higher risk of anemia and death during pregnancy and delivery. Intense whipworm infection in children may result in trichuris dysentery syndrome, the classic signs of which include growth retardation and anemia. Heavy burdens of both roundworm and whipworm are associated with protein-energy malnutrition.

Preventive Measures

Better sanitation reduces soil and water contamination with egg-carrying feces. Sanitation is the only definitive intervention to eliminate helminthic infections, but to be effective it should cover a high percentage of the population. *Ascaris lumbricoides* and *Trichuris trichiura* are primarily spread by ingestion of contaminated foods, water, and soils. With high costs involved, implementing this strategy

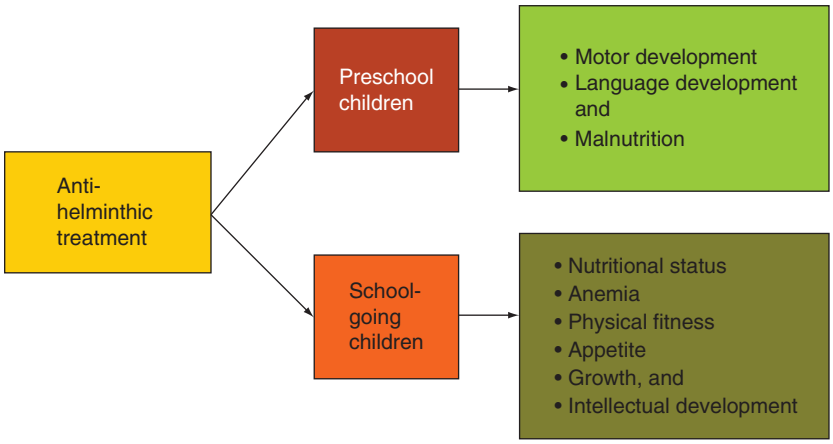

Figure 7 Anti-helminthic treatment and its effects on preschool and school-going children.

is difficult where resources are limited. Both the World Bank and WHO promote helminth control programs and consider the programs to be one of the most cost-effective strategies for improving health in developing countries. Wearing shoes, to prevent transmission of hookworms and *Strongyloides* through skin contact, has also been promoted.

Deworming

Recommended drugs for use in public health settings include benzimidazole anthelmintics, albendazole (single dose: 400 mg, reduced to 200 mg for children between 12 and 24 months), or mebendazole (single dose: 500 mg), as well as levamisole or pyrantel palmoate. Programs aim for mass treatment of all children in high-risk groups (communities where worms are endemic) with anthelmintic drugs every 3 to 6 months. Gulani and colleagues (2007) have estimated that deworming increases hemoglobin by 1.71 g/l (95% confidence interval 0.70 to 2.73), which could translate into a small (5–10%) but significant reduction in the prevalence of anemia.

Home delivery of antihelminthics is problematic for several reasons and thus school-based deworming programs are preferred. These have been shown to boost school participation and are practical as schools offer a readily available, extensive, and sustained infrastructure with a skilled workforce that can be readily trained. In Kenya, such a program reduced school absenteeism by a quarter, with the largest gains among the youngest children. Perhaps even more important, this study showed that those children who had not been treated benefited from the generally lowered transmission rate in the schools. Figure 7 depicts the antihelminthic treatment and its effects on preschool and school-going children.

These preventive measures must be coupled with community behavior change strategies with the aim of reducing contamination of soil and water by promoting the use of latrines and hygienic behavior. Without a change in defecation habits, periodic deworming cannot attain a stable reduction in transmission.

Table 17 Interventions and their effect on diseases

Major intervention	*Disease prevented or treated*
Effective antenatal care	Neonatal deaths, infections, pneumonia
Skilled maternal and neonatal care	Neonatal deaths, neonatal tetanus, infections
Maintenance of personal hygiene	Neonatal deaths, typhoid, diarrhea, infections
Drug treatment	Diarrhea, pneumonia, infections, typhoid, dengue, malaria, neonatal deaths, infections, meningitis
Vaccines	Pneumonia, typhoid, infections, meningitis
Oral rehydration therapy	Diarrhea
Vitamin A	Diarrhea, malaria
Zinc	Diarrhea, pneumonia, malaria
Water/sanitation/hygiene	Neonatal deaths, diarrhea, pneumonia, typhoid, helminth
Breast feeding	Diarrhea, pneumonia, infections, typhoid, neonatal deaths
Complementary feeding	Diarrhea, pneumonia, malaria, neonatal deaths
Intermittent preventive treatment in pregnancy	Malaria and other infections
Insecticide-treated nets	Malaria, dengue

Medical Treatment

The WHO recommends the use of albendazole, mebendazole, pyrantel, and levamisole. A review of the 14 studies showed that both benzimidazoles have high efficacy against roundworm and moderate efficacy against whipworm. Single-dose mebendazole is much less effective against hookworm, with cure rates typically below 60%.

Conclusions

The global burden of infectious diseases contributing to child mortality is considerable. The situation is further compounded by increasing antimicrobial resistance and

the emergence of newer infections with viruses such as avian influenza (H5N1) and severe acute respiratory syndrome (SARS). Although the contribution of neonatal infections to overall child mortality has only recently been recognized, the persistent global burden of deaths due to diarrhea and pneumonia underscores the need for improved public health strategies for change. We have interventions that can make a difference (**Table 17**) to childhood infectious diseases. What is needed is their implementation at scale to populations at greatest risk. This will require not only biomedical approaches but measures to address the social determinants of disease.

See also: Bacterial Infections: Overview; Dengue, Dengue Hemorrhagic Fever; Drinking Water and Sanitation; Gastrointestinal Disorders: Overview; The History of Malaria and its Control; Infant Mortality/Neonatal Disease; Protozoan Diseases: Cryptosporidiosis, Giardiasis and Other Intestinal Protozoan Diseases; Protozoan Diseases: Malaria Clinical Features, Management, and Prevention; Typhoid Fever; Water Pollution: Emerging Contaminants Associated With Drinking Water.

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