Global Child Health: Burden of Disease, Achievements, and Future Challenges

Melanie Rosenberg, MD

Children in developing countries are disproportionately affected by the worlds' diseases. Ninety percent of children under 5 years old live in the developing world. Over 10 million children under 5 die each year, most from preventable or treatable causes, and 90% of these deaths occur in only 42 of the world's countries.[1] While progress in reducing mortality has been made over the last several decades, an enormous discrepancy persists between mortality in industrialized and in developing countries (Fig 1).

In 2000, world governments together created the Millennium Development Goals as priority areas that needed to be addressed to eradicate poverty and promote development.[2] Included is the goal to reduce under-five child mortality by two-thirds by the year 2015. Unfortunately, progress toward this goal remains inconsistent. Based on data from 1990 to 2003, the World Health Organization (WHO) estimates that only 93 countries are "on track" to meeting the Millennium Development Goal for under-five mortality, and these were the countries that started out with the lowest mortality rates.[3] Even more concerning is that 29 countries are described as stagnating in progress, and 14 are in "reversal" (Table 1). There are several potential reasons behind the alarming halt in progress in some countries. The correlation of increasing or stagnating child mortality rates with conflict and humanitarian crisis is apparent. Also likely to be contributing are unabated high rates of poverty and high prevalence rates of human immunodeficiency virus (HIV), particularly in countries in sub-Saharan Africa.[4]

From the Pediatric Hospitalist Division, Children's National Medical Center, Washington, DC.
Curr Probl Pediatr Adolesc Health Care 2007;37:338-362
1538-5442/$ - see front matter

doi:10.1016/j.cppeds.2007.07.003

Causes of Child Morbidity and Mortality in the Developing World

The leading causes of child mortality are shown in Figure 2.[3] Of note, diarrheal disease and pneumonia together account for the most deaths, and these deaths are not due to pathogens unique to tropical climates but similar to those in the developed world. However, failures in prevention and treatment attributable to multiple factors result in much higher rates of mortality. There is significant geographical variation in distribution of causes of death (Fig 3).[3] Deaths due to HIV and malaria represent a much larger percentage in some countries in Africa. In countries with overall low mortality rates where the number of deaths from infectious disease is falling, neonatal deaths represent a greater overall proportion of total deaths in children under 5.

Risk factors for child mortality are associated with poverty and include lack of safe water, poor hygiene and sanitation, crowding, indoor air pollution, poor maternal nutrition, lack of exclusive breastfeeding in the first 6 months of life, malnutrition and micronutrient deficiencies, and recurrent infectious disease.[5] Malnutrition is estimated to contribute to over 50% of all child deaths, although it is rarely reported as a direct cause.[6] Indeed reporting of a single underlying cause of death in each child is likely an oversimplification, as many deaths may be multifactorial; both acquired immunodeficiency syndrome (AIDS) and measles can be complicated by diarrhea and respiratory infections.[1] The diseases most commonly implicated in contributing to child morbidity and mortality are described below.

Diarrhea and Dehydration

Despite advances in prevention and treatment, diarrhea continues to be a leading killer of young children, accounting for 17% of all under-five deaths.[3] The

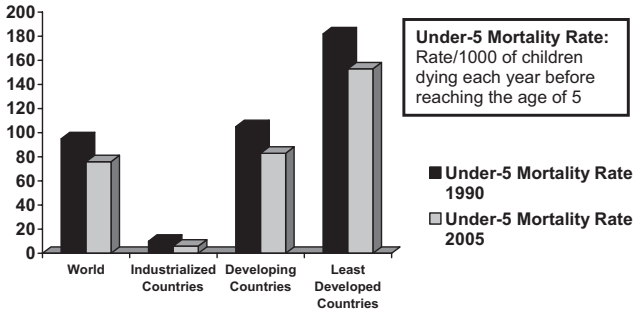

FIG 1. Global under-five mortality estimates, 1990 and 2005. Data from UNICEF Customized Statistical Tables derived from The State of the World's Children 2007. Accessed April 27, 2007. Available from: http://www.unicef.org/statistics/index_24183.html.

majority of these deaths occur in developing countries. Case fatality rates declined significantly from 13.6/1000 to 4.9/1000 from the 1970s to the 1990s; however, the incidence of acute diarrheal illness has not changed significantly, and the child under 5 in a developing country has an average of 3.2 episodes per year.[7]

Rotavirus is the most common single causative agent of diarrhea for the most severe diarrheal disease worldwide,[8] although bacterial pathogens are more prevalent in developing countries where poor hygiene and sanitation are still problems and fecal–oral spread is not prevented.[9] Rotavirus has been estimated to cause over 100 million cases of diarrhea each year, and up to 600,000 deaths in children under 5.[10] The incidence of disease in all countries is similar, although children in developing countries have much higher mortality rates, likely due to lack of clean water, decreased access to health care, and underlying malnutrition.[10] Unlike in temperate climates, rotavirus is found year-round in developing countries, and children in developing countries tend to get infected at an earlier age.[11] Other viruses such as adenovirus, astrovirus, and caliciviruses have been found worldwide, are also transmitted by the fecal–oral route, and contribute to a substantial proportion of childhood diarrhea.[11]

While rotavirus may have other forms of transmission such as through contact or fomites, bacterial pathogens are predominantly spread by the fecal–oral route, and therefore, poor hygiene and sanitation place children in developing countries at higher risk.[9] Bacterial pathogens that are important etiologies of childhood diarrhea include *Escherichia coli*, *Campylobacter*, *Shigella* spp, *Salmonella* spp, *Yersinia*, and *Vibrio cholerae*.[9,12] Enterotoxigenic *E. coli* is a common cause of acute, watery, noninflammatory diarrhea, as are enteropathogenic *E. coli*, *Campylobacter*, and *Salmonella*. Dysentery is diagnosed clinically on the basis of the presence of fever, bloody diarrhea, abdominal pain, and tenesmus. The most common cause of bacterial dysentery are *Shigella* spp, which may contribute to up to 15% of all mortality from diarrhea.[12] *Shigella* is estimated to cause 1 million deaths each year, 60% of which occur in children under 5.[13] *Salmonella*, *Campylobacter*, and *Entamoeba histolytica* must also be considered with this type of presentation. Cholera, and in particular *V. cholerae* serotypes O1 and O139, remains an important cause of epidemic diarrhea and is known for its potential to cause rapid volume depletion and death within 24 hours.[9] It is of particular importance in times of disaster or humanitarian crisis when crowding is common and sanitation is poor.[14]

TABLE 1. Progress toward reducing under-five mortality rates

Countries	U5MR 1990	More than 2 years in humanitarian crisis since 1992	Pattern of U5MR 1990-2003
93	59	3%	On track
51	92	20%	Slow progress
29	207	38%	Stagnating
14	111	57%	Reversing

U5MR, Under-five mortality rate.
Adapted from The World Health Report 2005: Making Every Mother and Child Count. Geneva: WHO; 2005. Table 1.1: Neonatal and maternal mortality in countries where the decline in child mortality has stagnated or reversed, p. 16 and Table 2.1: Factors Hindering Progress, p. 22.

Acute diarrheal illnesses are distinguished from persistent diarrhea, also referred to as postinfectious diarrhea, defined as diarrhea lasting longer than 14 days. Persistent diarrhea is multifactorial in origin and is commonly associated with underlying malnutrition and micronutrient deficiencies, inappropriate management of diarrheal illness including cessation of breastfeeding, early introduction of breast milk substitutes such as animal milk, and specific etiologic agents including *E. coli* and HIV-associated pathogens.[15] Despite being responsible for only a small percentage of all diarrheal episodes, it is associated with a disproportionately high mortality level, particularly when following an episode of dysentery.[16] Principles of management include rehydration, continued breastfeeding, micronutrient supplementation, and feeding with a low-lactose diet or substituting yogurt for milk. It is important to recognize and manage this syndrome

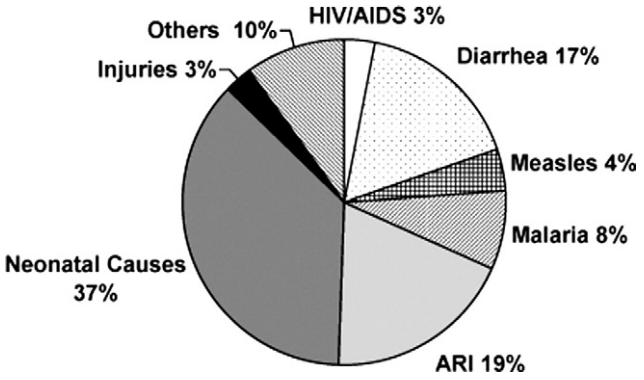

FIG 2. Estimates of under-five mortality by cause in WHO regions, 2000 to 2003. Adapted from data reported in: WHO. The World Health Report 2005 – Making Every Mother and Child Count. Statistical Annex Table 3. Annual number of deaths by cause for children under five years of age in WHO regions, estimates for 2000-2003. p. 190-1.

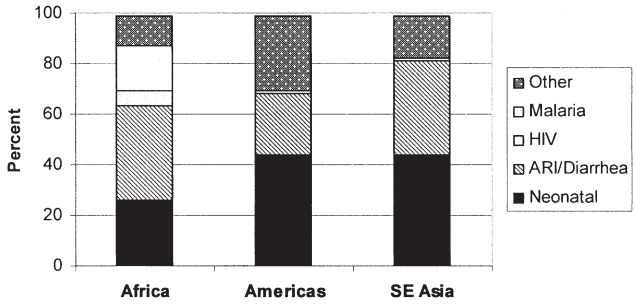

FIG 3. Distribution of causes of under-five deaths by WHO region. Adapted from data reported in: WHO. The World Health Report 2005 – Making Every Mother and Child Count. Statistical Annex Table 3. Annual number of deaths by cause for children under five years of age in WHO regions, estimates for 2000-2003. p. 190-1.

as distinct from etiologies of chronic diarrhea seen in developed countries.[15]

The profound decrease in diarrhea mortality over the last three decades can be linked to various factors including increased breastfeeding, improved nutrition, improved sanitation, and increased rates of measles vaccination.[7,9] However, because morbidity has not decreased substantially, the widespread implementation of oral rehydration therapy (ORT) has likely made the greatest contribution to the reduction in mortality.[7] ORT was introduced in the 1970s by WHO and has become the mainstay of treatment for diarrheal illness.[14] The development of this solution using specific concentrations of glucose and electrolytes was based on evidence that the sodium-coupled glucose transporter across the apical villous membrane in the intestine remains intact during episodes of infectious diarrhea, and uptake of water is maximized when sodium and glucose are present in appropriate proportions.[17] Use of ORT in cases of diarrhea increased dramatically by the 1990s, and estimated mortality dropped by about 75%.[18]

Recommendations for community management of diarrhea have evolved over the years. Based on the detrimental impact of diarrhea on nutritional status and evidence that feeding through the illness decreased mortality, continued feeding has been promoted in conjunction with rehydration, reversing previously held practices of withholding food during illness.[18] In addition, the use of the original ORT solution was challenged due to concerns of sodium concentrations in excess of what was needed to treat stool losses from noncholeric diarrhea,[12] and the lack of impact on stool output.[16] Based on these concerns, a new reduced-osmolar ORT solution with decreased sodium concentration was developed and is currently recommended by WHO and UNICEF.[19] In a meta-analysis of several trials, the reduced osmolarity solution was found to be associated with decreased need for intravenous hydration therapy, decreased stool output, and less frequent vomiting when compared with the original standard WHO formula.[20]

Antibiotic therapy is not recommended for routine treatment of diarrhea in the developing world. However, antibiotics can decrease duration of illness in shigellosis[21] and are therefore recommended in cases of dysentery when *Shigella* is suspected.[9] Unfortunately, *Shigella* has rapidly developed resistance to various antimicrobials commonly used to treat dysentery including ampicillin, cotrimoxazole, and tetracycline[13] and has resulted in increased use of fluoroquinolones such as ciprofloxacin due to low cost and availability.[16] Because resistance to fluoroquinolones is also developing and available treatment options are becoming yet further restricted, vaccine development is being strongly encouraged.[16,22]

Acute Respiratory Infections

Excluding neonatal deaths, pneumonia is the leading killer of children under 5 worldwide, despite the existence of effective prevention and treatment. Again, the burden falls predominantly on children in developing countries, with over 150 million episodes in children under 5 each year, and an estimated 2 million deaths.[23] Pneumonia accounts for 20% of under-five

deaths in the developing world, but only 2% in industrialized countries. This is not surprising, as poverty increases the risk of crowded living conditions, indoor air pollution, and malnutrition.[24]

Attributing cases of pneumonia to specific etiological agents is difficult even in developed countries; however, limited laboratory capacity in resource-poor settings makes it even more challenging, and consequently, accurate data on the etiologic agents of pneumonia is limited. However, studies have shown the most common pathogens are again not tropical diseases but the same as those that predominated in industrialized countries before universal immunization.[25] The leading cause continues to be *Streptococcus pneumoniae*, with *Haemophilus influenzae* being an important contributing pathogen, as well as *Staphylococcus aureus*. Among viral causes, respiratory syncytial virus has been shown to be the most common.[24] In regions where HIV prevalence rates are high, incidence of pneumonia may increase significantly, as children with HIV are at risk for opportunistic infections but also much higher risk for more common bacterial pathogens.[25]

Accurate diagnosis of pneumonia depends on physical examination findings, laboratory evaluation, and ultimately, a chest radiograph. However, access to pulse oximetry, radiologic studies with adequate interpretation, or even auscultation by a skilled health care worker is limited in most developing country settings. Because of this, WHO has developed very simple guidelines for diagnosing pneumonia based on clinical signs, with tachypnea being the most reliable indicator.[26] These guidelines, based on various studies, define pneumonia based on a respiratory rate of at least 50 in infants 2 through 11 months, and 40 for children 12 months to 5 years; lower chest in-drawing is used to signify children with more severe pneumonia requiring hospital admission. These guidelines are highly sensitive yet less specific for bacterial pneumonia,[26] since other febrile illnesses and viral infections can cause tachypnea as well. However, identification of children with pneumonia based on respiratory rate is useful for community workers to determine who should be treated with antibiotics and has been proven effective in detecting cases of bacterial pneumonia in community settings.[26]

Case management of pneumonia using the above guidelines has been shown to be extremely effective in decreasing mortality. A meta-analysis of community-based intervention trials in young children showed not only a 36% decrease in mortality caused by pneumonia, but also a 24% decrease in overall mortality in children under 5, and these findings were consistent across various countries.[27] Amoxicillin and cotrimoxazole are recommended as first-line treatment of non-severe pneumonia,[28] although bacterial resistance to cotrimoxazole is increasing.[26] Intramuscular antibiotic therapy (or intravenous where available) is recommended in cases of severe pneumonia. However, there is evidence from a randomized trial performed at sites in eight developing countries that oral amoxicillin was as effective as the WHO standard of intramuscular penicillin in treating severe pneumonia.[29] There is also evidence from several studies that 3 days of treatment with oral amoxicillin or cotrimoxazole is as effective as the standard empiric 5 days of treatment that has been recommended.[26,28] The implications of these studies are particularly important where cost and compliance are barriers to successful treatment.

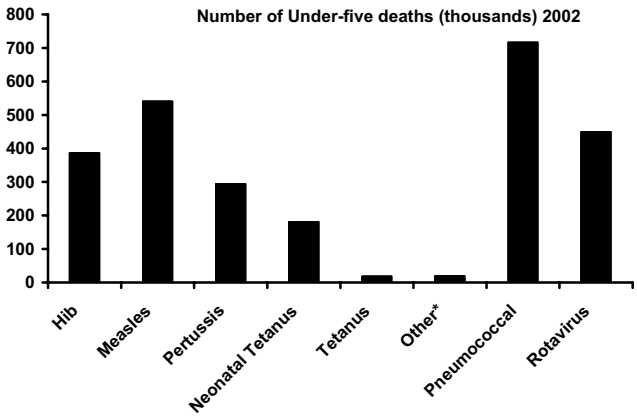

FIG 4. Under-five deaths caused by vaccine-preventable diseases 2002. Adapted from data reported in: WHO. Global Immunization Data. Geneva: WHO; 2004. Available from: http://www.who.int/immunization_monitoring/data/GlobalImmunizationData.pdf. Accessed April 27, 2007.

Vaccine-Preventable Diseases

Infections that are referred to as vaccine-preventable diseases, due to their eradication or near-eradication in many industrialized countries, are still significant causes of mortality. Figure 4 shows the number of deaths attributable to vaccine-preventable diseases in 2002. Among those infections for which immunizations have already been implemented on a global level, measles causes the most deaths in children worldwide, the vast majority occurring in developing countries.[30] The illness is highly contagious and almost all children without immunity will become infected.[31] Most chil-

TABLE 2. Reported incidence of vaccine-preventable diseases and estimated vaccine coverage, 1980 and 2005

	1980			2005		
	Estimated coverage (%)	Cases	Cases in DCs (%)	Estimated coverage (%)	Cases	Cases in DCs (%)
Diphtheria	20	97,774	>99	78	8229	>99
Measles	16	4,211,431	89	77	580,287	>99
Pertussis	20	1,982,384	97	78	121,799	72
Polio	22	52,795	>99	78	2033	100
Neonatal tetanus	7	13,005	>99	57	9782	100

DCs, Developing countries.
Adapted from data reported in: WHO Vaccine Preventable Diseases: Monitoring System. 2006 Global Summary. Geneva: WHO; 2006.

dren develop a self-limited illness characterized by cough, coryza, conjunctivitis, and a classic maculopapular rash. However, measles infection can affect nearly every organ system and can have serious sequelae.[32] Respiratory complications are the leading cause of mortality and include pneumonia, caused by measles or a secondary viral or bacterial infection, and laryngotracheobronchitis. Case-fatality rates are higher among children in developing countries compared with industrialized countries, due to malnutrition, vitamin A deficiency, and lack of access to care.[32]

While some vaccine-preventable diseases such as pertussis are reemerging in industrialized countries, many are now diseases found solely in the developing world, and elimination remains a challenge despite the existence of effective vaccines. The bacteria that cause tetanus are found worldwide and can affect children of all ages, although neonatal tetanus is the most common presentation.[31] WHO estimates that neonatal tetanus still caused 180,000 deaths in the year 2002.[33] Infants present within the first week or two of life with poor feeding, emesis, and spasms that can be confused with convulsions.[34] Intensive care is required for effective respiratory support and management of spasms and dysautonomia; however, these resources are often not available and mortality from neonatal tetanus is high. Prevention of neonatal tetanus relies not only on maternal immunization, but also on clean delivery methods and sanitary cutting of the umbilical cord; therefore, lack of access to skilled delivery in clean settings increases risk for disease.[35]

Vaccines for measles, polio, diphtheria, pertussis, tetanus, and BCG have been included in the WHO Expanded Program on Immunization since 1974 and have been universally adopted in national immunization programs.[36] A standard immunization schedule developed in 1984 is widely used in developing countries[31] and includes BCG immunization at birth, three doses of DPT and oral polio vaccines commonly administered at 6, 10 and 14 weeks, and one measles immunization which is often given at 9 months of age. Hepatitis B vaccine was introduced in 1992. Since this program was launched, coverage in infants worldwide has increased from less than 25% to greater than 75% in some cases, and dramatic reductions in disease incidence were achieved (Table 2). Of these infections, polio is closest to being eradicated, with only six countries identified as endemic in 2005.[37]

Despite great achievements, it is clear from reviewing the data that declines in mortality stagnated in the early to mid-1990s as rates of coverage reached a plateau. Three doses of DPT vaccine (DPT3) have been used by UNICEF as an indicator of vaccine coverage: in 2005, an estimated 28 million infants still were not adequately immunized.[37] WHO also recommends that all children have a "second opportunity" for measles vaccination. The initial measles vaccine is given at 9 months of age, due to evidence for higher attack rates and increased disease severity in young infants in developing countries, but early vaccination is associated with decreased rates of seroconversion.[38] Although the number of countries offering a second dose increased by 2005, through either routine or targeted supplemental immunization activities, many countries in Africa and South Asia were still not providing the second dose.[39] Increasing coverage of primary immunization in the first year of life as well as second immunization opportunities for all children is likely needed to further reduce measles mortality.

Immunization against *H. influenzae* b (Hib) was recommended for routine use in developing countries in the 1990s[36] and by 2005 had been introduced in 101 countries.[37] Infection by this organism causes an estimated 386,000 deaths each year, with the highest disease burden in infants 4 to 18 months old, and is the dominant cause of nonepidemic bacterial meningitis in infants worldwide.[40] Hib vaccine is extremely effec-

tive and has led to virtual elimination of invasive disease in many parts of the world.[40] Similar efficacy in eliminating invasive disease has also been shown in The Gambia.[41] In addition several studies in developing countries have shown a reduction in cases of radiographically confirmed pneumonia associated with introduction of Hib vaccine.[26] Barriers to introducing the vaccine in countries in Africa and Southeast Asia, where uptake has been slow, include cost of the vaccine combined with lack of sufficient evidence of disease burden in many countries, partly caused by limited diagnostic capabilities.[42]

As mortality from many vaccine-preventable diseases is reduced, infections such as pneumococcal disease and rotavirus which are not yet included in most national immunization programs account for a greater proportion of mortality (Fig 4).[33] However, there is now evidence that similar dramatic reductions in mortality from these diseases are possible. The 7-valent conjugated pneumococcal vaccine (PCV-7) has been shown in the United States to significantly decrease the incidence of invasive disease and also decrease incidence of radiographically proven pneumonia.[26] Because the 7-valent vaccine lacks certain serotypes thought to contribute to invasive disease in developing countries, 9-valent and 11-valent vaccines have been studied.[43] In a study in The Gambia, a 9-valent pneumococcal vaccine was demonstrated to decrease cases of pneumonia by 37%, invasive pneumococcal disease from vaccine serotypes by 77%, and all-cause mortality by 16%.[44] Similar reductions in incidence of pneumonia and invasive disease were demonstrated in a study in South Africa.[45] Based on this evidence, WHO recently published a position paper recommending that PCV-7 be considered a priority for inclusion in all national immunization programs.[43]

The development of safe and effective rotavirus vaccines now means that rotavirus can be included in global disease prevention strategies. Two recent large-scale clinical trials of new rotavirus vaccines showed efficacy against infection, as well as 85 to 98% efficacy against severe rotavirus gastroenteritis.[46,47] In addition, the vaccine studied in 11 Latin American countries was found to decrease hospitalization rates for diarrhea from all causes by 42%.[47] These vaccines are already being licensed and implemented in the United States and other countries. Prevention of rotavirus in developing countries where high mortality from diarrhea exists could obviously have an enormous public health impact. Challenges to implementation include vaccine cost and lack of data regarding local disease burden in many countries.[48] In addition, similar to the problems encountered with other live oral vaccines such as poliovirus and cholera, previous trials of rotavirus vaccines found them to be less immunogenic and protective in African countries than in the United States or Latin America, raising concerns that the effectiveness of the new vaccines in other regions of the world cannot be accurately predicted and that further trials in low-income countries are needed.[48]

Malaria

An estimated half billion cases of malaria occur each year, resulting in 1 million deaths, the vast majority occurring in sub-Saharan Africa.[49] While under-five mortality from other causes has decreased over the past several decades, child mortality due to malaria has increased during the 1980s and 1990s.[49] As demonstrated in Figure 3, malaria was estimated to account for almost 20% of under-five deaths in Africa in 2002. The observed increase in mortality can be attributed to a combination of factors that have led to setbacks in malaria control: increasing resistance to antimalarial drugs and insecticides, war and civil unrest, breakdown of health care infrastructure and control programs, increasing travel and migration, and increasing HIV prevalence which affects both immune susceptibility and the capacity of health care facilities.[49,50]

Of the four types of malaria parasites, *Plasmodium falciparum* continues to be the leading cause of severe disease and mortality. Malaria usually presents as a nonspecific febrile illness, often leading often to misdiagnosis and confusion with other infections.[51] Young children are particularly vulnerable to severe malaria, which can include respiratory distress, hypoglycemia, severe anemia, acidosis, and coma. Severe malarial anemia, resulting from acute and recurrent infections, contributes substantially to child mortality from malaria in sub-Saharan Africa.[52] Cerebral malaria is a common and well-known complication of *P. falciparum* malaria in young children, manifesting as fever, altered mental status/coma, and seizures, and may be difficult to distinguish clinically from bacterial meningitis. It is associated with a high mortality rate[51] as well as high risk of neurological impairment and seizure disorder for those that do survive.[53]

In addition to the unacceptably high child mortality caused by malaria, the disease also has indirect effects, particularly among children in highly endemic areas who have frequent repeated infections. The impact on child health begins in pregnancy; malaria infection in pregnant women increases risk of low birth weight and prematurity.[54] Recurrent infections in childhood can result in chronic anemia, impaired growth and cognition, and decreased educational attainment and productivity.[49] In addition, recurrent episodes of febrile illness result in decreased appetite, further worsening the cycle of malnutrition and infection.[54]

Since clinical presentation cannot be relied on for accurate diagnosis, confirmatory blood tests are recommended. Evaluation of thick and thin blood smears is still considered the gold standard, but this remains a challenge in locations with limited resources as it relies on maintenance of equipment and skilled review of slides.[50,51] Rapid diagnostic tests have been developed and implemented in some areas. These new tests are advantageous because they require minimal skill to interpret results and they perform well in tropical climates; however, widespread implementation has been limited due to cost.[50]

Malaria control is dependent on multiple interventions including vector control, prevention with insecticide-treated nets or spraying, accurate diagnosis, treatment with effective antimalarials, and control of epidemics. Drug resistance has become an enormous barrier to eliminating malaria. In Asia and Africa, high rates of resistance to chloroquine led to the introduction sulfadoxine-pyrimethamine, to which resistance also rapidly developed. This led to the formulation of new and innovative combination therapies primarily with artemisin derivatives, which have been shown to be highly effective against *P. falciparum* malaria.[50] WHO now recommends use of artemisin combination therapies in all areas where there is chloroquine resistance.[49] However, use of these new medications is limited by cost, limited available supply, and lack of pediatric formulation.[55]

Vector-control using insecticides reduces malaria transmission by both repelling and killing mosquitoes.[56] Insecticide-treated bed nets are promoted as a mainstay of malaria prevention in most endemic countries.[49] A review of five large randomized studies in Africa showed that they reduced malaria episodes, protected against severe disease, and reduced child mortality by 17%.[57] The original bed nets required retreatment every 6 months, which proved logistically challenging,[56] and cost of nets to families has been an obstacle to widespread utilization unless they are subsidized.[50] Long-lasting insecticide-treated bed nets which remain effective for 4 to 5 years have been developed and are being implemented as an alternative.[49,58] Indoor residual spraying with long-lasting insecticides have been used effectively to eradicate malaria in many regions of the world including parts of South Africa[58]; however, spraying declined in use due to cost, concerns for insecticide resistance, lack of community acceptability, and safety concerns of using DDT.[59] However, based on known effectiveness in reducing child mortality and cost-effectiveness, WHO is now promoting spraying as a primary method of prevention for all endemic regions, including Africa, and is supporting the use of the insecticide DDT as a safe method when used appropriately for public health measures rather than agriculture.[60]

Intermittent preventive therapy is recommended during pregnancy in regions with high, stable transmission rates of *P. falciparum* malaria.[56] The administration of sulfadoxine-pyrimethamine to women during pregnancy has been shown in several studies to decrease maternal anemia and incidence of low birth weight.[61] In Malawi, adoption of intermittent preventive therapy for all pregnant women resulted in a reduction in low birth weight from 23 to 10% among women who received at least two doses of sulfadoxine-pyrimethamine.[62] Intermittent preventive therapy with antimalarials for infants is a relatively new intervention in which medications are administered in conjunction with routine immunizations. Studies performed in Tanzania, where malaria infection occurs year round, showed significant reduction in rates of malaria attacks, with more modest but still considerable reductions found in other countries where transmission is more seasonal.[63] While these reports are encouraging, more research is needed to address concerns of decreased natural immune response and "rebound effect" as well as potential for drug-resistance if implemented on a large scale.[64,65]

HIV

The HIV epidemic has dealt a major blow to progress in decreasing under-five mortality worldwide, and again the burden is greatest in sub-Saharan Africa. In severely affected countries in sub-Saharan Africa such as Zimbabwe and Botswana where adult HIV prevalence is high, AIDS accounted for over one-third of deaths in children under five during 2002

to 2005,[66] and these countries have been categorized as reversing progress in their overall child mortality rates since 1990.[3] In sub-Saharan Africa, it is estimated that 2 million children are infected with HIV, with 1500 new cases in children under 15 every day; an additional 170,000 in Asia are infected and slightly over 100,000 in the rest of the world.[66] Several hundred thousand children with AIDS die each year in sub-Saharan Africa.[66] Studies on the natural history of HIV infection in untreated children in Africa show much higher rates of mortality in the first 2 to 3 years of life than in industrialized countries.[67,68] This rapid progression to death is attributed not only to lack of available antiretroviral treatment but also to higher burden of infectious diseases and lack of access to health care.

HIV infection is not only important in its impact on mortality rates but also creates devastating conditions for surviving children. Children are at risk of losing parents to HIV and being orphaned, losing teachers and health care workers to HIV, developing psychological trauma due to social isolation and discrimination, and living in poverty due to lack of a working adult to care for them.[69] In addition, an enormous burden is placed on health care systems and health care personnel, many of whom are affected by HIV themselves.[3]

The vast majority of childhood infections occur through perinatal transmission. It is estimated that without any intervention, 15 to 30% of HIV-positive mothers will transmit the infection to their infants during pregnancy and delivery, with an additional 10 to 20% transmission occurring through breastfeeding.[70] Access to highly active antiretroviral therapy for the mother as well as safe breast milk substitutes in high-income countries has allowed rates of perinatal acquisition of infection to drop to less than 2%, compared with 20% in low- and middle-income countries.[66] While neither highly active antiretroviral therapy nor safe breast milk substitutes are available to most women in developing countries, other methods exist specifically for preventing transmission. Antiretrovirals to prevent mother-to-child transmission are highly effective and cost-effective in high-prevalence areas. The use of zidovudine or zidovudine plus 3TC during the antenatal, intrapartum, and postpartum periods or single-dose nevirapine administered during labor and then to the infant after delivery significantly reduces rates of HIV transmission to infants.[71,72] Unfortunately, only about 10% of HIV-positive mothers in developing countries currently have access to this important intervention.[70]

Given the known risk of postnatal transmission through breast milk, research has been to done to examine the relative risks and benefits of breastfeeding by HIV-positive mothers. In industrialized countries where access to breast milk substitutes and clean water is assured, it is recommended that HIV-positive women do not breastfeed. However, in some developing countries, mixed breastfeeding, defined as early introduction of solids or non-breast-milk liquids (water or formula), actually increases mortality in infancy compared with exclusive breastfeeding, possibly due to bacterial contamination of foods and reduced positive effects of breast milk.[73,74] Mixed breastfeeding has been associated with increased risk of HIV transmission, although the reasons for this are unclear.[73,75] Based on this and other evidence, and a general lack of safe breast-milk substitutes in much of the developing world, a recent consensus statement by WHO recommends exclusive breastfeeding by HIV-positive mothers for the first 6 months *unless* replacement feeding is "acceptable, feasible, affordable, sustainable, and safe."[76]

Effective antiretroviral therapy exists for treating pediatric HIV; however, only one in eight children needing antiretroviral therapy in developing countries was receiving it in 2006.[66] Numerous barriers exist to scaling up treatment for children with HIV that will not likely be solved quickly.[77] These include cost of the medications, lack of available pediatric formulations, and limited diagnostic capabilities for diagnosing HIV in infancy. In addition, there are inadequate numbers of health care professionals trained in pediatric HIV in the highest prevalence countries; many have been lost to work in higher income countries or to death from HIV infection.[77]

Tuberculosis

Despite the enormous burden of disease that exists in the world among both children and adults, tuberculosis (TB) is often omitted from discussions of child mortality. However, there is evidence that childhood TB is on the rise in many countries.[78] Approximately 1 million cases occur in children under 15 each year, accounting for about 10% of total TB cases, although in some countries up to 25% of TB cases occur in children.[79] In industrialized countries, cases of TB in children primarily occur in high-risk populations, including immigrants from endemic areas,[78] and these

cases represent only a small proportion of the total cases worldwide. Risk factors for TB infection include poverty, crowded living conditions, and malnutrition,[80] so it is not surprising that the burden is greatest in the poorest countries.

Children with TB can initially be asymptomatic and go undiagnosed; those who manifest symptoms most commonly present with prolonged fever, weight loss, and chronic cough.[81,82] Unlike reactivated tuberculosis which is the form most often seen in adults, children often present with primary pulmonary tuberculosis. They also commonly present with extrapulmonary manifestations including lymphadenitis, abdominal, spinal, and pericardial disease.[83] Children less than 5, and particularly those less than 2, are at higher risk for developing disease after infection, and specifically disseminated miliary TB and TB meningitis, which are associated with higher morbidity and mortality.[78]

Accurate diagnosis of tuberculosis in children is challenging for several reasons,[79,83] and even more so in locations with limited resources. Young children commonly present with extrapulmonary TB, making microbiological diagnosis less probable. Pulmonary disease in children tends to be noncavitary forming and paucibacillary, and young children cannot produce adequate cough effort to expectorate sputum, so the likelihood of a positive smear for acid-fast bacillus is unlikely. Because of this, gastric aspirates are the method of choice for isolating the organism from young children; however, since sensitivity of the smear is low, this method relies on ability to perform mycobacterial culture, which is unavailable in most developing countries.[83] Chest radiograph and tuberculin skin test both can be useful aids in diagnosing TB, but availability and accurate interpretation are barriers to widespread use in the developing world.[79,83] Due to these diagnostic challenges, attempts have been made to develop algorithms or scoring systems to detect cases, but they have not been uniformly adopted or proven effective.[83] Recently, the WHO Stop TB Partnership published guidelines on defining cases of both smear-negative and smear-positive in TB in children, as well as a recommended approach to diagnosis.[79] Because these guidelines include chest radiograph, tuberculin skin testing, and microscopy, their applicability in resource-poor settings will continue to be limited and diagnosis will continue to be a challenge.

WHO recommends that BCG vaccine be given at or shortly after birth in countries where risk of TB infection is high. As of 2005, an estimated 83% of the world's children were vaccinated in 156 countries.[30] While variable results in protection against TB infection have been found, the vaccine has been estimated to be effective in decreasing cases of meningitis and disseminated TB by 64 and 78%, respectively.[84] The vaccine is most effective in Africa and Asia, where rates of disease as well as coverage are high.[85] However, the vaccine has not had an impact on rates of adult infection, and therefore, has not changed the disease from a public health perspective.[83]

TB and HIV

The double burden of TB and HIV coinfection has become a significant public health problem in both children and adults. While reported rates of coinfection in children are variable, existing data in several southern African countries show that childhood cases of TB are increasing,[78] which may be related to high prevalence of HIV in those countries. Coinfection has numerous implications for surveillance, diagnosis, and treatment. Infection with HIV and subsequent immunosuppression further impedes accurate diagnosis of TB as the tuberculin skin test is often falsely negative. HIV is the most important factor increasing risk of TB.[86] Coinfection with HIV has been associated with more rapid progression of TB infection, poorer compliance with medication regimens, increased relapse rates, and increased mortality.[81,83] In addition, TB may be difficult to distinguish clinically or radiographically from other HIV-related lung diseases[81] and HIV-infected children may be infected with multiple pathogens, which may lead to over- or underdiagnosis depending on the level of suspicion.[78] Coinfection makes the eradication of TB in endemic countries an even greater challenge, due to increased risk for transmission, increased treatment failure rates, and the possibility of development of more resistant TB.[86]

Malnutrition and Micronutrient Deficiencies

Malnutrition and specific micronutrient deficiencies are well-known for their role in childhood disease worldwide. Protein-energy malnutrition and multiple micronutrient deficiencies commonly coexist in children who have deficient calorie intake characterized by unvaried diets.[87] Lack of overall nutrition leads to marasmus, characterized by loss of subcutaneous fat and muscle tissue, whereas protein deficiency with relatively good caloric intake leads to kwashiorkor, manifested by edema, hair and skin changes, hepato-

megaly, and lethargy.[88] Most commonly children present on the spectrum between the two, referred to as marasmic kwashiorkor.[87]

Different anthropometric measurements are used to describe malnutrition. Stunting, or linear growth retardation, represents a delay in skeletal growth, is an indicator for chronic malnutrition, and is often associated with recurrent infections. Wasting is indicative of an acute weight loss or failure to gain weight, associated with an acute infection, food shortage, or other crisis situation.[88] Weight-for-age is a composite indicator of both acute and chronic malnutrition[89] and is the most commonly used indicator of child nutritional status.[90] Stunting, wasting, and underweight are defined as height-for-age, weight-for-height, and weight-for-age, respectively, that are less than −2 standard deviations below the median value for the reference population.[90]

Severe acute malnutrition is defined as weight-for-height <70% of the median or at least 3 SD below reference values (severe wasting), the presence of bilateral pitting edema, or a mid-upper-arm circumference <110 mm.[89] In resource-poor settings where health care workers skilled at performing measurements may not be available, the mid-upper-arm circumference provides a reliable indicator of malnutrition[89]; alternatively, visible wasting can be used to make the diagnosis.[91] These children can also be recognized based on the presence of severe edema, skin changes, lightened hair color, and extreme apathy.[87] Children with severe acute malnutrition should always be assessed for dehydration and infection, although both of these can be difficult to detect, as affected children will have decreased subcutaneous tissue and are less likely to mount a fever.[91] Severe acute malnutrition is associated with high case-fatality rates, up to 20 to 30%, and in many places this has not changed, possibly due to the complexities involved in treatment and the potential for iatrogenic complications.[89]

While 10% of children in developing countries are severely wasted, another 26% are estimated to be moderately to severely underweight and 31% are stunted.[92] Analysis of available data shows that the majority of child deaths attributable to malnutrition are due to moderate malnutrition.[6] Malnutrition is not identified as a direct cause of mortality in conventional statistics, because another primary cause of death is usually recorded; however, estimates have been made of the impact of malnutrition on mortality. In a review of data from 10 countries comparing weight-for-age with risk of death from common infectious diseases in children 5 and under, 53% of deaths could be attributed to malnutrition, an estimate that was consistent with previous studies.[6] Further analysis by specific disease revealed a strong association between degree of malnutrition and risk of mortality from diarrhea, especially from dysentery, as well as from acute respiratory infections and malaria, while the evidence for measles was less consistent.[93] Extrapolated to global statistics, malnutrition contributes to approximately 5,000,000 deaths in young children each year.

TABLE 3. Prevalence of malnutrition in world regions

	% of infants with low birthweight, 1998-2005*	% of under-fives (1996-2005*) suffering from: underweight, moderate and severe	% of under-fives (1996-2005*) suffering from: stunting, moderate & severe
Latin America and Caribbean	9	7	15
South Asia	29	45	44
Sub-Saharan Africa	14	28	37

Reproduced from UNICEF Customized Statistical Tables derived from The State of the World's Children 2007. Accessed May 10, 2007. Available from: http://www.unicef.org/statistics/index_24183.html.

Prevalence of low birth weight, underweight, and stunting in different regions is shown in Table 3. Numerous factors contribute to this persistently high prevalence of poor nutrition and growth and starts with the health of the mother.[87] Malnutrition is of course directly related to poverty, as it is impacted by low maternal education, lack of available child care, and lack of food security.[88] Poor maternal nutrition will increase the risk for low birth weight and for decreased stores of micronutrients passed on to the infant. Early discontinuation of breastfeeding, inappropriate introduction of solid foods, and use of breast milk substitutes are all contributing factors. According to UNICEF data from 1996 to 2004,[92] only 36% of infants were exclusively breastfed until 6 months of age. Nonbreastfed infants have also been found to be at much higher risk of dying from acute respiratory tract infection and diarrhea than breastfed infants.[94] Infants who are not breastfed not only lose the nutritional and immunologic benefits but may be exposed to contaminated water or food sources, since access to clean water for making formula and cleaning bottles or cups may be limited.

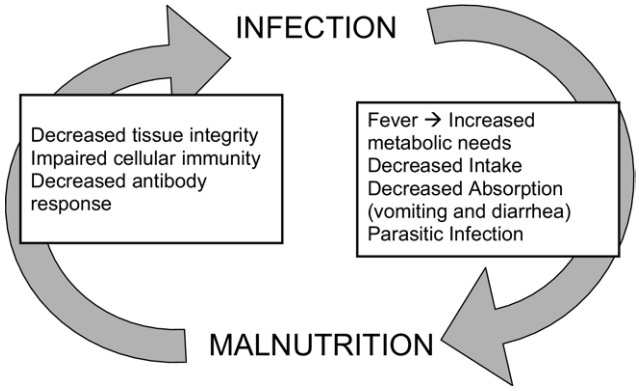

FIG 5. The cycle of infection and malnutrition.

Complementary foods, which should be added to ongoing breastfeeding at 6 months of age, are often introduced in ways that provide insufficient nutrition. Sometimes the foods chosen are not are provided in adequate quantities, are introduced too early leading to displacement of breastfeeding, or are not stored or prepared hygienically.[95] Even when appropriate in quantity and timing, complementary foods such as cereals may be lacking in necessary micronutrients, and animal products may not be available.[96]

Malnutrition has a synergistic and cyclical relationship with infection as illustrated in Figure 5. It is common for children in developing countries to have recurrent, frequent infections, and these contribute to deterioration in nutritional status in various ways, not only through decreased energy intake, but also through gastrointestinal losses of nutrients, increased catabolism resulting in protein loss, and gastrointestinal or urinary losses of micronutrients such as zinc, copper, and vitamin A.[97] The impact of these recurrent infections depends on the child's nutritional status at onset of infection, the child's diet during convalescence, and the degree to which the child has recovered at onset of the next infection.[97] Infection and fever decrease appetite in all children; however, due to cultural beliefs and practices, nutrient-rich foods may also be withheld during times of illness, resulting in further deterioration of nutritional status.[87] Conversely, as demonstrated in Figure 5, malnutrition adversely affects various components of the immune system, reducing the ability to fight infection and resulting in increased severity of infections.

The increased risk for mortality associated with malnutrition is likely related to simultaneous presence of multiple micronutrient deficiencies.[6] Micronutrient deficiencies play an important role in susceptibility and response to disease in children. Common threads in these deficiencies include poor maternal nutrition leading to poor infant stores, early weaning, and dependence on a monotonous diet consisting of a carbohydrate (legume, tuber) without adequate meat or plant sources.[87] The micronutrient deficiencies described below are the most pervasive.

Vitamin A deficiency is the leading preventable cause of blindness in children in the developing world. It results from a diet lacking in adequate plant and animal products which contain vitamin A,[88] as well as a lack of fat, which results in impaired vitamin A absorption.[87] An estimated 100 to 140 million children are affected.[98] Vitamin A deficiency results in a wide spectrum of ocular disease, ranging from poor dark adaptation and "night blindness," progressing to conjunctival and corneal xerosis and ultimately keratomalacia and blindness.[87] Measles infection associated with vitamin A deficiency increases the risk of these complications.[32] Vitamin A deficiency has also been associated with stunting,[99] although supplementation has not consistently been shown to have a significant effect on growth.[100] In addition, vitamin A deficiency contributes to anemia through complex mechanisms and is necessary for functioning of the immune system.[99]

Based on studies using supplementation, vitamin A deficiency is considered a significant risk factor for mortality from diarrheal illness, measles, and malaria.[99] Vitamin A supplementation has been shown to have significant effects on mortality in both prevention and treatment of disease. When given every 4 to 6 months, vitamin A supplementation has been shown to decrease mortality in children 6 months to 5 years of age by 23%, primarily by reducing deaths due to diarrhea and measles.[101,102] Based on this evidence, vitamin A supplementation is recommended to be given every 4 to 6 months for children 6 to 59 months and has commonly been integrated into national immunization programs and other child health activities.[103] Large doses (200,000 IUs) given for two consecutive days to children with measles infection has been shown to decrease mortality by over 50% and specifically mortality due to pneumonia in measles,[104] although no effect has been found in treating non-measles pneumonia.[105] Treatment doses are therefore recommended for all children with measles, severe malnutrition, or ocular complications of vitamin A deficiency.[106] UNICEF estimates that, in 2003, 76%

of children in the least developed countries received vitamin A supplementation.[98]

Iodine is required by the thyroid gland for synthesis of hormones thyroxin and triiodothyronine. Because thyroid hormone is essential for central nervous system development in early life, maternal iodine deficiency results in severe and irreversible neurological sequelae in the infant, including mental retardation and motor disturbances such as spasticity and rigidity.[107] This is referred to as endemic cretinism and is the leading cause of preventable mental retardation in children worldwide.[108] Iodine deficiency in childhood and adolescence can also lead to goiter, hypothyroidism, and mental impairment, with significant consequences for intellectual development and productivity.[87]

Most diets are deficient in iodine due to its depletion from the soil, unless seafood or iodine-fortified food products are included in the diet.[88] Inland regions such as the Himalayas and Andes, where water derived from melted mountain snow leaches iodine from the soil, are particularly affected, as are flood plains regions. Because of its low cost, availability, and use in almost all foods, salt fortified with iodine has been the most widely used method of eliminating iodine deficiency.[87] While progress has been made in fortification, 54 countries are still classified as mildly to severely iodine-deficient, and WHO estimates that one-third of the world's schoolchildren suffer from insufficient iodine intake.[108]

The importance of zinc deficiency in childhood disease and mortality has become increasingly recognized. Zinc is a required component in multiple enzymes and proteins and plays an essential role in cellular metabolism and growth.[109] Deficiency arises from low intake of zinc-replete animal products, combined with high consumption of cereals and legumes that inhibit zinc absorption.[87,109] There is some evidence that zinc deficiency impacts physical growth,[109] and supplementation may have a modest effect on linear growth.[110] Studies on zinc supplementation also suggest that cognitive development may be affected, although the evidence is not consistent.[111] Zinc deficiency is difficult to measure accurately in individuals. However, trials of zinc supplementation have consistently shown a profound impact on morbidity and mortality from diarrheal disease as well as respiratory illnesses, suggesting that zinc plays a crucial role in combating infection and that deficiency is a major contributor to child mortality. A review of 10 trials performed in developing countries showed that zinc supplementation provided daily for at least 2 weeks resulted in decreased incidence of both diarrhea and pneumonia in children.[112] There is also some evidence that zinc supplementation decreases incidence of malaria, although this was based on data for health facility visits only.[113] When used to treat diarrheal illness, zinc supplementation resulted in decreased duration of symptoms as well as a reduction in mortality or treatment failure of 42% in persistent diarrhea.[114] There is also evidence that treatment with zinc hastens recovery from severe pneumonia.[115]

Zinc is not stored in the body as long as vitamin A, so more frequent supplementation is necessary[112] and the optimal method for supplementation or fortification has not yet been determined.[110] However, based on the evidence for decrease in mortality from diarrhea, WHO now recommends zinc supplementation for 10 to 14 days as an integral component of treating diarrheal illness, combined with ORT and continued feeding.[19] Implementation has not yet been widespread as with vitamin A, as challenges exist in formulation and production, and more research on cost-effectiveness, use with ORT, and compliance with different formulations is needed.[113]

Nutritional rickets is a worldwide problem and can result from low calcium intake, vitamin D deficiency, or both. Particularly at risk are infants who are solely breastfed for prolonged periods without vitamin D supplementation, and children who are weaned from breast milk to a calcium-deficient diet.[87] Risk factors for rickets vary by geographic location and population. In certain regions such as South Asia, the high prevalence of rickets is attributed to darker skin color combined with low sun exposure resulting in vitamin D deficiency, in addition to dietary factors, while in Africa low calcium intake and dietary inhibitors of absorption are common with vitamin D levels often being normal.[116] In Kenya, children with rickets were found to be consuming little or no animal or dairy products, and their primary cereal component contained high levels of phytates and oxalates, which impede absorption of calcium and other nutrients.[87]

Iron deficiency contributes significantly to perinatal mortality in the developing world, due to complications of anemia during childbirth.[117] Hemorrhage is one of the leading causes of maternal mortality worldwide[118] but predominantly affects women in Africa and Southeast Asia.[117] For children, direct effects on health outcomes are not related to infection or in-

creased mortality but stem from the long-term cognitive sequelae arising from chronic iron deficiency anemia. Diets limited to carbohydrates and lacking in meats and vegetables leave millions of children in the developing world at risk for iron deficiency. Increased needs for iron during early childhood, adolescence, and pregnancy place these groups particularly at risk.[88] Iron deficiency is estimated to account for about 50% of anemia in childhood.[111] Numerous other factors compound the burden of anemia in children, including other micronutrient deficiencies, recurrent infections with malaria, and chronic infection with soil-transmitted helminths.

Iron fortification of various food products has decreased the prevalence of anemia in many countries.[90] However, where this is not feasible, supplementation has been used. Because many children will likely be deficient in not one but multiple micronutrients, strategies at providing supplementation of multiple micronutrients as an acceptable food additive such as dissolvable tablets, sprinkles, or foodspreads have been developed.[119] Micronutrient sprinkles added to food in the home that included iron as well as vitamin A and zinc were shown to be acceptable to families and effective in correcting anemia in Ghana.[120] A large-scale multicenter trial of daily multiple micronutrient supplementation using dissolvable tablets added to food in the home was more effective in reducing anemia than iron supplementation alone, which is not surprising as other vitamin deficiencies likely contribute to anemia.[121] Finally, while supplementation may be feasible and effective, dietary diversification is the best long-term solution to micronutrient deficiencies, although it is also the most challenging strategy given the need for behavior change and improved food security.[90]

Parasitic Diseases

While most international efforts and funding have been aimed at the "big three" diseases, HIV/AIDS, malaria, and TB, increasing attention is being focused on neglected tropical diseases because of the enormous burden they inflict on years of life lost to disability rather than death.[122] The most common of these infections, schistosomiasis and three soil-transmitted helminths (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworms), are particularly relevant to child health. All of these diseases are highly endemic in developing countries, especially sub-Saharan Africa, and have significant geographic overlap, and children are commonly infected with multiple parasites.[122] The epidemiology of these infections differs from other common causes of childhood illness described above, in that the peak intensity of infection occurs in older children aged 5 to 15.[123] A high burden of hookworm infection is generally attained by adolescence and can continue into adulthood.[124]

The transmission mechanisms and clinical manifestations of these infections have considerable overlap.[123,125] In all three soil-transmitted helminth infections, the adult parasite inhabits the gastrointestinal tract; hookworm and ascariasis affect the small intestine, whereas trichuriasis affects the large intestine. Transmission to others occurs by passage of eggs in the stools, which are then transmitted by ingestion, or in the case of hookworm, by larval penetration of the skin.[125] Schistosomiasis is acquired by direct penetration of the skin from contaminated water where snails serve as intermediate hosts, and eggs are then shed in human urine and feces.[126] A primary risk factor for acquisition and transmission of these infections is therefore contact with contaminated soil or water, which is directly related to poverty, poor sanitation, and lack of access to clean water.

These infections cause relatively few deaths each year so their impact is less reflected in mortality rates than in morbidity, measured by disability-adjusted life-years. Of these infections, hookworm is responsible for the greatest number of disability-adjusted life-years lost, primarily due to iron-deficiency anemia from gastrointestinal blood loss.[124] Trichuriasis can further exacerbate anemia through gastrointestinal losses, and schistosomiasis can contribute as well through urinary (*Schistosoma haematobium*) or intestinal (*Schistosoma mansoni*) losses. Large parasite burdens in ascariasis can lead to intestinal obstruction but can also cause chronic malabsorption of vitamin A and other nutrients and lead to decreased appetite and food intake, and hookworm can cause significant protein losses.[125] The end result of coinfection with these parasites is therefore chronic anemia and nutritional deficits. There is substantial evidence that these infections contribute to impairment of growth and cognitive development in children and thus have important long-term consequences if not prevented or treated.[122] These infections are not only symptoms of poverty, but they perpetuate it as well, by hindering educational performance and ultimately economic productivity.[122]

Although improved sanitation is the only way to completely eliminate soil-transmitted helminth infections, providing periodic antihelmintic therapy can be highly effective in reducing morbidity and transmission.[124] Studies have shown that providing antihelmintic treatment can improve physical growth as well as cognitive development.[124] A strategy has been adopted by WHO to provide school-age children with regular periodic deworming, without confirming infection status, in addition to targeting high-risk groups such as preschool children and pregnant women.[127] Treatment must be repeated regularly due to high reinfection rates, up to two to three times per year in communities with high disease prevalence or intensity.[127] Drugs recommended for treatment of soil-transmitted helminths include albendazole and mebendazole due to their safety and low cost, and praziquantel as the first choice for schistosomiasis.[127] Because of their safety, these medications can be given in health facilities or in schools to reach the most children and have been integrated with immunization and vitamin A supplementation as well as school feeding programs.[128] Deworming campaigns are already underway in many countries, although it is estimated only 10% of schoolchildren are being reached, far from the stated goal of 75%.[129] Given that low-cost and safe drugs are now available, many as large-scale donations from pharmaceutical companies, further opportunities exist for using a coordinated package of three or four medications to treat the majority of neglected tropical diseases and dramatically reduce the cumulative morbidity from these diseases.[122]

Impaired Cognition

For those children who survive early childhood, it is clear that a combination of factors including protein energy malnutrition, micronutrient deficiencies, and chronic and recurrent infections put these children at risk for significant morbidity. In addition to the impact on health and physical growth, the effect on cognitive development has become a focus of research and has been acknowledged as a priority in international child health.[130-132] Impaired cognitive development is an epidemic in itself and likely contributes to the cycle of poverty and disease in many parts of the world.

In a review of studies done in developing countries, both degree of stunting as an indicator of malnutrition and level of poverty were consistently associated with decreased school achievement, cognitive scores, or literacy, depending on the outcome measured.[130] Based on available data on the prevalence of stunting and poverty among children under 5, the authors estimated that over 200 million children are at risk for not reaching their developmental potential by age 5, with the highest prevalence of disadvantaged children in sub-Saharan Africa and South Asia.[130]

Adequate nutrition is essential for mental development, and the highest risk period is between the second trimester of pregnancy and 2 years of age.[133] Nutrition therefore begins with the mother; poor maternal nutrition increases risk of intrauterine growth restriction and low birth weight, which can impair cognitive development well into childhood.[131] Malnutrition during the first year of life can have long-lasting consequences. In a longitudinal study comparing children diagnosed with marasmus or kwashiorkor in their first year of life with healthy controls, children with histories of malnutrition scored significantly less on IQ testing as far out as 11 to 18 years of age.[134] These results were significant even when controlling for the effects of environmental factors. Further support for the role of malnutrition in impaired cognitive development comes from randomized controlled trials showing consistent improvement in developmental outcomes when food supplements were provided, particularly if such an intervention is combined with early cognitive and psychosocial stimulation.[131,132] In a prospective study of Jamaican children 9 to 24 months of age who were stunted, both food supplementation and play stimulation had significant effects on mental development, but the greatest effect was seen when these interventions were combined.[135] This provides evidence that malnutrition clearly contributes to impairment of cognitive development, but that other household and environmental factors are important as well.

The contributions of specific micronutrient deficiencies are discussed above, with iodine deficiency being a well-established cause of cognitive deficits and the role of zinc less well-defined. The detrimental effect of iron deficiency on long-term cognitive development has been repeatedly demonstrated.[131] Several plausible mechanisms exist for impairment of cognition.[136] Anemia impairs normal development of the central nervous system. In addition, anemic children may seek less stimulation from their environment and from their caretakers, resulting in "functional isolation." Lozoff and colleagues followed infants with chronic iron

deficiency and non-iron-deficient controls up to 19 years.[137] The children who had iron-deficiency in infancy started with lower cognitive scores, and despite adequate iron supplementation, these children did not catch up to their counterparts and continued to show poorer cognitive scores until adulthood, with the most dramatic gap among the lower socioeconomic families demonstrating that nutrition interacts with other factors in its effect on child development. The study did not however show a benefit of iron supplementation once iron deficiency is diagnosed. In a meta-analysis of randomized controlled trials performed in developing countries, iron supplementation was found to have inconsistent effects on developmental outcome, with the primary benefits being reduction of preexisting deficits or prevention of further losses.[138]

Other factors contribute to poor cognitive development. Some are related to lack of access to health care and immunizations, including sequelae from recurrent otitis media and from central nervous system infections including bacterial meningitis and encephalitis.[131] The role of intestinal helminths is discussed above as a contributing factor. Cerebral malaria, which most commonly affects young children, has been estimated to cause neurological sequelae in several thousand children in Africa each year[53] and in a prospective study was found to result in a 3.7-fold increased risk of cognitive impairment.[139] HIV infection is known to cause encephalopathy and increases risk of developmental delay even without severe disease.[131] Children in developing countries are also at high risk for environmental exposures. Lead toxicity can result from exposure to contaminated soil or gasoline,[133] while exposure to toxic levels of arsenic and manganese in contaminated water supplies affects millions of people worldwide.[131]

Hearing impairment is an important risk factor for impaired language and cognitive development and represents another silent epidemic in the developing world that goes largely unnoticed due to lack of resources available for detection in young children. An estimated 700,000 infants will develop hearing impairment each year in the developing world.[140] Due to lack of access to health care, lower immunization rates, and decreased resources at health care facilities, infants in developing countries are at increased risk for congenital infections known to cause hearing loss, acquired infections such as measles, mumps, meningitis, and otitis media, complications from birth asphyxia and prematurity, exposure to ototoxic drugs, and sequelae from untreated neonatal jaundice.[140]

Finally, the effects of psychosocial factors including decreased stimulation in the home, maternal depression, and exposure to conflict and violence must be considered. As all these factors are interrelated, causality of any one factor is difficult to establish.[133] Poverty, poor nutrition, low level of maternal education, decreased stimulation, micronutrient deficiencies, and poor hygiene leading to parasitic infections all are likely to exist in the same household. Impaired cognitive development is likely multifactorial in origin and more research and attention are required to address this insidious and often overlooked epidemic.

Neonatal Morbidity and Mortality

While progress has been made on reducing under-five mortality, the neonatal mortality rate, defined as deaths occurring in the first 28 days, has not declined proportionately. Child mortality has declined by one-third since 1980, but neonatal mortality has dropped only by one-quarter, and the discrepancy between high-income countries and low- to middle-income countries continues to grow. Neonatal deaths now are estimated to account for 38% of all under-five deaths worldwide,[141] and in regions such as South Asia, up to 50%.[142] This brief 28-day period therefore holds much higher risk of mortality than the rest of a child's first 5 years of life. The reason for this discrepancy is related to the causes of newborn deaths, which are distinctly different from the causes of death in children older than 1 month of age.

Distribution of causes of neonatal deaths for the years 2000 to 2003 is shown in Figure 6. Among infectious causes, sepsis and pneumonia account for the majority of deaths, while 7% are still caused by neonatal tetanus.[141] Infections predominate as the cause of death in the late neonatal period, while deaths from preterm birth and birth asphyxia predominate during the first week.[142] The risk of death is greatest during the first week and particularly during the first 24 hours of life. Poor maternal nutrition leading to delivery of low birth weight infants is an important risk factor; similar to malnutrition, low birth weight is not described as a direct cause of death but is estimated to be implicated in up to 80% of neonatal deaths.[142] Meanwhile, for each neonatal death, up to 20 surviving newborns suffer from complications from

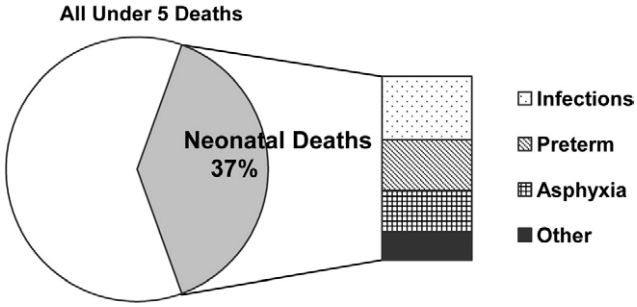

FIG 6. Causes of neonatal deaths, WHO estimates, 2000 to 2003. Adapted from data reported in: WHO. The World Health Report 2005 – Making Every Mother and Child Count. Statistical Annex Table 4. Annual number of deaths by cause for neonates in WHO regions, estimates for 2000-2003. p. 190-1.

these same conditions.[3] Children surviving preterm birth or birth asphyxia are more likely to have cerebral palsy or other debilitating problems for which little treatment is available in countries with limited resources.

Many countries have seen significant drops in their neonatal mortality rates specifically attributed to maternal tetanus immunization, and globally, deaths from neonatal tetanus have dropped by 50% since 1990.[141] However, community interventions such as immunization cannot be used to address the majority of neonatal deaths that occur during the first week of life. Deaths during this time period can largely be attributed to lack of skilled care during delivery and the immediate postpartum period. In sub-Saharan Africa and South Asia where neonatal mortality rates are the highest, only one-third of women deliver in the care of a skilled health care worker.[143]

While it may be perceived that universal access to intensive care facilities and advanced technology is necessary to decrease neonatal mortality worldwide, this is unlikely to be true. Reduction in neonatal mortality occurred in industrialized countries before the introduction of expensive technology; instead, effective, low-cost interventions including skilled care during labor, antibiotics, use of aseptic techniques, basic neonatal resuscitation, and early exclusive breastfeeding were likely responsible.[144] Some developing countries have shown similar progress. Sri Lanka dramatically decreased its neonatal mortality rate throughout the country by committing resources to providing easy and equitable access to skilled care by trained midwives, at government facilities where care is free.[144] For most low- and middle-income countries, however, scaling up skilled care at delivery remains a great challenge.

Maternal Health

This strategy of increasing access to skilled care is imperative to decreasing maternal mortality and morbidity as well. The timing of maternal deaths strongly mirrors that of neonatal deaths; while risk exists from the third trimester as far as 6 to 12 months postpartum, most pregnancy-related deaths occur in the first 1 to 2 days after birth,[118] further strengthening the argument for improved care during and after delivery. Causes of maternal mortality are diverse and vary between regions; however, in a review of maternal mortality data WHO found that hemorrhage, hypertensive disorders, and infection together account for at least 50% of all maternal deaths in developing countries.[145] These conditions are often not predictable and require skilled management to improve outcomes. Preventable diseases such as malaria, HIV, and anemia also contribute indirectly to maternal death. Finally, the continued practice of unsafe abortions, with the highest rates occurring in Latin America, accounts for 68,000 maternal deaths each year and likely causes significant morbidity and disability.[3]

Stillbirths occurring in the last 12 weeks of pregnancy are strongly related to maternal mortality. An estimated 3 million stillbirths occur each year,[146] which is equivalent to the number of neonatal deaths occurring in the first week of life. These numbers are staggering, yet these deaths go largely unrecorded despite being attributed to similar risk factors as maternal and early neonatal deaths. Combined, maternal deaths, neonatal deaths, and stillbirths total almost 8 million deaths each year,[3] the vast majority of which could be prevented with access to simple, low-technology interventions during pregnancy and the peripartum period.

Providing Interventions that Work

In 2003, as part of the Child Survival Series published in *The Lancet*, Jones and others identified over 20 interventions effective in decreasing newborn and child mortality based on extensive review of literature and expert opinion.[147] The vast majority of these interventions are preventive in nature, and many have been shown to impact mortality caused by multiple diseases.

For example, breastfeeding has been shown to have a significant protective effect against death from diarrhea and acute respiratory infections, particularly in the first months of life.[94,148] Complementary feeding programs that provide food supplementation combined with education and counseling have been proven to improve nutritional status and therefore likely contribute to decreasing mortality from various infectious causes.[149]

The public health impact of improved sanitation and hygiene on reducing disease in industrialized countries is well known. Interventions such as hygiene education, hand-washing promotion, improved sanitation, and improved water quality have proven effective in decreasing diarrheal illness.[150] A review of water and sanitation interventions also found significant decreases in incidence of trachoma and ascariasis, reductions in severity of various parasitic diseases including hookworm, and an overall 55% reduction in child mortality.[151] A recent study performed in squatter settlements in Karachi, Pakistan implementing intensive promotion of hand-washing with plain soap showed not only a 53% reduction in incidence of diarrheal illness, but also a 50% reduction in cases of pneumonia in children under 5.[152] This was a labor-intensive intervention requiring provision of free soap and weekly promotion activities, therefore having limited feasibility for expansion, yet illustrates that simple, low-cost interventions once adopted can effectively prevent the diseases that cause the greatest mortality in young children.

Many of the other disease-specific interventions supported in the Child Survival Series are presented above, including ORT and zinc supplementation for treatment of diarrhea, immunizations, vitamin A supplementation, prevention of malaria using insecticide-treated bed nets, and community management of pneumonia. Since the publication of the Child Survival Series, evidence continues to grow for yet more successful interventions that could greatly impact mortality in the developing world, including new vaccines for pneumococcal disease and rotavirus, a growing body of evidence on micronutrient supplementation to prevent and treat disease, and intermittent preventive therapy for prevention of malaria in infants. The benefits of these interventions are further amplified when the impact on morbidity, health care utilization, and cognitive development of children is considered.

Integrated Approaches

Many of the interventions described above, all effective individually, have been implemented as distinct initiatives or "vertical programs," which places a large burden on the health care infrastructure to provide systems for each separate intervention. This approach to implementing interventions also poses a challenge each time a new intervention is to be added. To address this problem, WHO and UNICEF introduced the Integrated Management of Childhood Illnesses (IMCI) strategy in the 1990s.[153] An integrated approach was proposed to improve case management by health care workers, promote efficiency, and increase cost-effectiveness. Based on the IMCI strategy,[154] health workers at outpatient facilities are trained to recognize symptoms of the most common illnesses including pneumonia, diarrheal illness and dehydration, malaria, measles, and acute or chronic otitis media, using simple examination techniques such as respiratory rate, skin turgor, and body temperature. Clinical recognition of conditions such as malnutrition and anemia is also included. Patients with danger signs, such as coma, convulsions, severe wasting, or anemia, are given initial treatment and are then referred to a hospital. Patients without severe illness are treated based on their diagnosis with effective interventions including ORT, antibiotics, and antimalarials. Micronutrient supplementation, deworming, nutritional counseling, and review of immunization status are included in the guidelines, so that opportunities for one effective intervention are not missed if the child accesses the health care system for a different problem, and parental counseling on how to manage illness at home is emphasized. Clinical challenges have arisen with these guidelines, such as the exclusion of infants during the first week of life, during which there is a high mortality rate,[144] and the high prevalence of HIV in many communities, which alters the epidemiology and clinical presentation of infectious disease.

As of 2002, IMCI had been adopted by over 100 countries.[153] The impact of the program has been studied rigorously in five countries. The greatest success was found in Tanzania where IMCI implementation was associated with strengthened health systems and high utilization rates of health care facilities.[153] Studies showed that children in IMCI districts in Tanzania received better care, including better assessment by a health care provider and increased likelihood of receiving correct treatment,[155] and the pro-

gram was associated with a 13% reduction in under-five mortality.[156]

Although these results were promising, they have not been replicated in all countries,[157,158] and a large-scale impact from IMCI has not yet been demonstrated.[153] The initial evaluation revealed that four of the five countries had difficulty scaling up to a national level while maintaining quality of the program.[159] Challenges to large-scale successful implementation reflect common barriers to improving health care in developing countries and included high staff turnover rates, low staff motivation due to low salaries in some countries, poor supervision, lack of hospital resources available for referral of sick patients, and low utilization rates of health care facilities.[153]

Achieving Universal Coverage

It has been estimated that over 60% of under-five deaths could be prevented if universal coverage were achieved with known effective interventions, and this estimate did not include newer tools such as rotavirus vaccine.[147] Unfortunately, despite the vast body of evidence supporting these effective and low-cost interventions, many children do not benefit from them. Estimates of coverage of interventions in the year 2000 for the 42 countries bearing 90% of the burden of child mortality reveal discouraging trends.[147] Breastfeeding was the only intervention estimated to reach almost all children. Measles vaccine was estimated at only 68% coverage; vitamin A supplementation was estimated at only 55%, and ORT was estimated at only 20%. Coverage with Hib vaccine was estimated at 1% and treatment of diarrhea with zinc at 0%, showing the enormous delay in getting evidence applied where it is needed. A subsequent analysis of the 60 countries with the highest child mortality showed similar results.[160] While there was great variability between countries and some had high coverage specifically for immunizations and breastfeeding, proven interventions such as ORT and antimalarial treatment were at less than 50% coverage, and prevention of maternal-to-child transmission of HIV and use of insecticide-treated bed nets had each achieved only 3% median coverage levels.

Why is higher coverage so difficult to achieve? Factors that have been implied in reaching coverage levels include strong political commitment, availability of human resources, and commitment of financial resources.[160] Since the 1990s, the child survival movement has lost momentum toward meeting internationally defined goals. Renewed leadership and commitment of financial and human resources are needed, and because child survival interventions are often competing with initiatives to fight AIDS, malaria, and tuberculosis, sector-wide approaches that integrate these different initiatives have been suggested.[161] Finally, greater attention must be paid to the widening disparities in health care and outcomes, not only between countries but within them as well, if further reductions in child mortality are to be realized.

Inequities in Child Health

For child survival interventions, low coverage rates are not the entire story, as they do not reflect the staggering inequities within countries, between urban and rural populations, and between poor and rich families. Ideally, the poorest, most at-risk children would have greatest access to effective interventions, but this is not the reality. In an analysis of coverage with eight proven interventions, including immunization, skilled care at delivery, access to safe water and vitamin A supplementation, substantial differences in coverage were found in all countries between the poorest and wealthiest families.[162] Statistically significant associations were found between wealth quintile and likelihood of receiving interventions. In some countries, such as Haiti and Cambodia, children in the poorest quintile were over 10 times less likely to receive at least six of the eight interventions than children in the wealthiest quintile. In countries with high overall coverage, the poorest quintile was disproportionately affected, while in countries with the lowest overall coverage, the wealthiest disproportionately benefited.

Similar discrepancies in access to pregnancy-related care have been found. Inequities exist in all countries based on socioeconomic status regarding access to antenatal care, facility-based birthing, and access to skilled care at delivery, and even in countries with high overall coverage, the poorest women are less likely to benefit from these services.[3] Both maternal mortality rates[118] and neonatal mortality rates[141] have been shown to be inversely related to the wealth of the family.

These patterns of inequity are consistent and pervasive. Within a given country, risk of death before reaching age 5 is greater among poor children.[5] Malnutrition is increased in poorer households in sub-Saharan Africa as well as rural areas compared with urban areas.[163] Differences in care-seeking have

also been found. In rural Tanzania, children from wealthier families were more likely to be brought for care to treat illness and more likely to receive antibiotics or antimalarials.[164] This pattern is confirmed by UNICEF data showing that seeking care for a child with suspected pneumonia is more likely in urban versus rural locations as well as among families in higher wealth quintiles.[23]

It is not surprising that differences in nutritional status, care-seeking behavior, access to interventions, and mortality are related to poverty. Poverty impacts health systems as well as geographic and economic access to health services. Basic water and sanitation as well as nonpolluting indoor fuels may not be available to the poorest populations, and transportation and health care costs may prohibit seeking care. The direct relationship of poverty to decreased maternal education is also a factor. Mothers with decreased education may be less knowledgeable about using clean water, providing nutritious foods, and seeking health care for signs of illness.[5] Decreased maternal education has been associated with higher risk for being underweight and lower likelihood of receiving immunizations.[165]

New interventions tend to reach the wealthier populations first, referred to as the principle of inverse equity, so that a lag in time to adoption of child survival activities by certain countries may lead to delay in reaching the poorest children.[162] A study of IMCI implementation showed that, after the initial pilot period, the program did not equitably reach the poorest populations, and in some countries did not reach the areas with greatest need at all.[166] Pursuing universal coverage of known interventions is therefore not enough, and adding new interventions when such disparities already exist increases the risk that these tools will simply reach the same children who already have access, and not the poorest children who are being excluded.[162] The tools for saving lives already exist, but implementation strategies are needed that ensure that new vaccines and other interventions more quickly reach the neediest populations.

Conclusions

Great progress has been made in reducing child mortality over the last several decades, and advances in prevention and management of disease have also contributed to decreasing morbidity and improving the quality of lives of children. The HIV epidemic, emergence of resistance against antibiotics and antimalarials, and the high number of children living in war or crisis situations means that infectious diseases will continue to cause significant illness and death among children, particularly in sub-Saharan Africa, and that these complex problems cannot be addressed rapidly. However, for the vast majority of deaths in infants and children, effective and low-cost methods of prevention and treatment exist, but coverage remains suboptimal. In addition, continued promotion of community-based interventions alone will not address the millions of newborn deaths each year. Strengthening of health systems and human resources to ensure that all women can have skilled care at delivery is a much greater challenge but is needed if newborn survival is to improve alongside child survival. Finally, as health care around the globe improves, disparities widen and the poorest, neediest individuals continue to be denied access to services that should be universally accessible. There is still great progress to be made in applying knowledge to practice, and ensuring that all children have the same opportunity to survive the first years of childhood, to grow up healthy, and to achieve their full developmental potential.

References

1. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? Lancet 2003;361:2226-34.
2. United Nations. General assembly, 56th session. Road map towards the implementation of the United Nations millennium declaration: report of the Secretary-General (UN document no. A/56/326). New York: United Nations, 2001 [cited June 20, 2007]. Available from: http://www.un.org/documents/ga/docs/56/a56326.pdf.
3. WHO. The World Health Report 2005: Making Every Mother and Child Count. Geneva: WHO, 2005 [cited April 27, 2007]. Available from: http://www.who.int/whr/2005/en/.
4. UNICEF. Progress for Children. A Child Survival Report Card. Vol 1. New York: UNICEF, 2004 [cited May 2, 2007]. Available from: http://www.unicef.org/publications/index_23557.html.
5. Victora CG, Wagstaff A, Schellenberg JA, Gwatkin D, Claeson M, Habicht JP. Applying an equity lens to child health and mortality: more of the same is not enough. Lancet 2003;362:233-41.
6. Caulfield LE, de Onis M, Blossner M, Black RE. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. Am J Clin Nutr 2004;80:193-8.
7. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. Bull World Health Organ 2003;81:197-204.

8. Glass RI, Parashar UD, Bresee JS, Turcios R, Fischer TK, Widdowson MA, et al. Rotavirus vaccines: current prospects and future challenges. Lancet 2006;368:323-32.
9. Podewils LJ, Mintz ED, Nataro JP, Parashar UD. Acute, infectious diarrhea among children in developing countries. Semin Pediatr Infect Dis 2004;15:155-68.
10. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003;9:565-72.
11. Hart CA, Cunliffe NA, Bresee, JS. Diarrhoea caused by viruses. In: Cook GC, Zumla, A, editors. Manson's tropical diseases. 21st Edition. London: Elsevier Science; 2003. p. 823-30.
12. Cheng AC, McDonald JR, Thielman NM. Infectious diarrhea in developed and developing countries. J Clin Gastroenterol 2005;39:757-73.
13. Kotloff KL, Winickoff JP, Ivanoff B, Clemens JD, Swerdlow DL, Sansonetti DJ, et al. Global burden of Shigella infections: implications for vaccine development and implementation of control strategies. Bull World Health Organ 1999;77:651-66.
14. Thapar N, Sanderson IR. Diarrhoea in children: an interface between developing and developed countries. Lancet 2004; 363:641-53.
15. Bhutta ZA. Post-infectious persistent diarrhoea. In: Southall D, Coulter B, Ronald C, Nicholson S, Parke S, editors. International child health care: a practical manual for hospitals worldwide. 1st Edition. London: BMJ Books; 2002. p. 283-6.
16. Keusch GT, Fontaine O, Bhargava A, Boschi-Pinto C, Bhutta, ZA, Gotuzzo, E, et al. Diarrheal diseases. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al, editors. Disease control priorities in developing countries. 2nd Edition. New York: Oxford University Press; 2006. p. 371-88 [cited May 10, 2007]. Available from: http://www.dcp2.org/pubs/DCP.
17. Sentongo TA. The use of oral rehydration solutions in children and adults. Curr Gastroenterol Rep 2004;6:307-13.
18. Victora CG, Bryce J, Fontaine O, Monasch R. Reducing deaths from diarrhoea through oral rehydration therapy. Bull World Health Organ 2000;78:1246-55.
19. WHO. Implementing the new recommendations on the clinical management of diarrhea: guidelines for policy makers and programme managers. Geneva: WHO, 2006 [cited May 22, 2007]. Available from: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/ISBN_92_4_159421_7.htm.
20. Hahn S, Kim Y, Garner P. Reduced osmolarity oral rehydration solution for treating dehydration due to diarrhoea in children: systematic review. BMJ 2001;323:81-5.
21. Salam MA, Bennish ML. Antimicrobial therapy for shigellosis. Rev Infect Dis 1991;13(Suppl 4):S332-41.
22. Niyogi SK. Shigellosis. J Microbiol 43:133-43, 2005.
23. UNICEF. Pneumonia: The Forgotten Killer of Children. New York: UNICEF, 2006 [updated September 2006; cited 2007 April 25]. Available from: http://childinfo.org/areas/ari/.
24. Cashat-Cruz M, Morales-Aguirre JJ, Mendoza-Azpiri M. Respiratory tract infections in children in developing countries. Semin Pediatr Infect Dis 2005;16:84-92.
25. Schuchat A, Dowell SF. Pneumonia in children in the developing world: new challenges, new solutions. Semin Pediatr Infect Dis 2004;15:181-9.
26. Simoes EAF, Cherian T, Chow J, Shahid-Salles S, Laxminarayan R, John TJ. Acute respiratory infections in children. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al, editors. Disease control priorities in developing countries. 2nd Edition. New York: Oxford University Press; 2006. p. 483-97 [cited 2007 May 10]. Available from: http://www.dcp2.org/pubs/DCP.
27. Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. Lancet Infect Dis 2003;3:547-56.
28. WHO. Technical updates of the guidelines on Integrated Management of Childhood Illness (IMCI): evidence and recommendations for further adaptations. Geneva: WHO; 2005 [cited 2007 April 27]. Available from: http://www.who.int/child-adolescent-health/publications/IMCI/ISBN_92_4_159348_2.htm.
29. Addo-Yobo E, Chisaka N, Hassan M, Hibberd P, Lozano JM, Jeena P, et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. Lancet 2004;364:1141-8.
30. WHO. WHO vaccine-preventable diseases: monitoring system. 2006 Global Summary. Geneva: WHO; 2006 [cited 2007 April 25]. Available from: http://www.who.int/vaccines-documents/DocsPDF05/WHO_IVB_2005.pdf.
31. Brenzel L, Wolfson L, Fox-Rushby J, Miller MA, Halsey NA. Vaccine-preventable diseases. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al, editors. Priorities in developing countries. 2nd Edition. New York: Oxford University Press; 2006. p. 389-411 [cited 2007 May 10]. Available at: http://www.dcp2.org/pubs/DCP.
32. Perry RT, Halsey NA. The clinical significance of measles: a review. J Infect Dis 2004;189(Suppl 1):S4-16.
33. WHO. Global Immunization Data. Geneva: WHO; 2004 [cited 2007 April 25]. Available from: http://www.who.int/immunization_monitoring/data/GlobalImmunizationData.pdf.
34. Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. Br J Anaesth 2001;87:477-87.
35. Vandelaer J, Birmingham M, Gasse F, Kurian M, Shaw C, Garnier S. Tetanus in developing countries: an update on the maternal and neonatal tetanus elimination initiative. Vaccine 2003;21:3442-5.
36. Centers for Disease Control (CDC). Vaccine preventable deaths and the Global Immunization Vision and Strategy, 2006-2015. MMWR Morb Mortal Wkly Rep 2006;55:511-5.
37. WHO. Progress towards Global Immunization Goals - 2005: Summary presentation of key indicators. Geneva, 2006 [cited 2007 May 19]. Available from: http://www.who.int/immunization_monitoring/data/SlidesGlobalImmunization.pdf.
38. World Health Organization (WHO). Measles Vaccines. WHO Position Paper. Wkly Epidemiolog Rec 2004;79:130-43.
39. Wolfson LJ, Strebel PM, Gacic-Dobo M, Hoekstra EJ, McFarland JW, Hersh BS. Has the 2005 measles mortality

reduction goal been achieved? A natural history modelling study. Lancet 2007;369:191-200.
40. World Health Organization (WHO). Position Paper on Haemophilus Influenzae type b conjugate vaccines. Wkly Epidemiolog Rec 2006;81:445-52.
41. Adegbola RA, Secka O, Lahai G, Lloyd-Evans N, Nije A, Usen S, et al. Elimination of Haemophilus influenzae type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study. Lancet 2005;366:144-50.
42. WHO. Selected vaccine introduction status into routine infant immunization worldwide. Geneva: WHO; 2003 [cited 2007 June 20]. Available from: http://www.who.int/immunization_monitoring/routine/schedule_analysis_2003.pdf.
43. WHO. Pneumococcal conjugate vaccine for childhood immunization—WHO position paper. Wkly Epidemiolog Rec 2007;82:93-104.
44. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 2005;365:1139-46.
45. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003;349:1341-8.
46. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006;354:23-33.
47. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354:11-22.
48. Glass RI, Bresee JS, Turcios R, Fischer TK, Parashar UD, Steele AD. Rotavirus vaccines: targeting the developing world. J Infect Dis 2005;192(Suppl 1):S160-6.
49. WHO, UNICEF. World Malaria Report 2005. Geneva: WHO, 2005 [cited 2007 April 27]. Available at: http://www.rbm.who.int/wmr2005/html/toc.htm.
50. Greenwood BM, Bojang K, Whitty CJ, Targett GA. Malaria. Lancet 2005;365:1487-98.
51. Summer AP, Stauffer WM, Fischer PR. Pediatric malaria in the developing world. Semin Pediatr Infect Dis 2005;16:105-15.
52. Murphy SC, Breman JG. Gaps in the childhood malaria burden in Africa: cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and complications of pregnancy. Am J Trop Med Hyg 2001;64(Suppl 1-2):57-67.
53. Mung'Ala-Odera V, Snow RW, Newton CR. The burden of the neurocognitive impairment associated with Plasmodium falciparum malaria in sub-saharan Africa. Am J Trop Med Hyg 2004;71(Suppl 2):64-70.
54. Roll Back Malaria, WHO. Children and Malaria. Roll Back Malaria Information Sheet [cited 2007 June 20]. Available from: http://www.rbm.who.int/cmc_upload/0/000/015/367/RBMInfosheet_6.htm.
55. John CC. Pediatric malaria: defining the problem, devising solutions. Presented at Pediatric Academic Societies' Annual Meeting. Toronto; 2007.
56. Breman JG, Mills A, Snow RW, Mulligan J, Lengeler C, Mendis K, et al. Conquering malaria. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al, editors. Disease control priorities in developing countries. 2nd Edition. New York: Oxford University Press; 2006. p. 413-31 [cited 2007 May 19]. Available from: http://www.dcp2.org/pubs/DCP.
57. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev 2004;(2):CD000363.
58. Lengeler C, Shapr B. Indoor Residual Spraying and Insecticide-treated Nets. In: Reducing Malaria's Burden: Evidence of Effectiveness for Decision-Makers. Washington, DC: Global Health Council; 2003 [cited 2007 May 20]. Available from: http://www.globalhealth.org/view_top.php3?id=384.
59. WHO Global Malaria Programme. Indoor residual spraying: Use of indoor residual spraying for scaling up global malaria control and elimination. WHO Position Statement. Geneva: WHO; 2006 [cited 2007 May 20]. Available from: http://malaria.who.int/docs/IRS-position.pdf.
60. WHO. WHO gives indoor use of DDT a clean bill of health for controlling malaria. News release. Washington DC; 2006 [cited 2007 May 20]. Available from: http://www.who.int/mediacentre/news/releases/2006/pr50/en/index.html.
61. Vallely A, Vallely L, Changalucha J, Greenwood B, Chandramohan D. Intermittent preventive treatment for malaria in pregnancy in Africa: what's new, what's needed? Malar J 2007;6:16.
62. Rogerson SJ, Chaluluka E, Kanjala M, Mkundika P, Mhango C, Molyneux ME. Intermittent sulfadoxine-pyrimethamine in pregnancy: effectiveness against malaria morbidity in Blantyre. Malawi, in 1997-99. Trans R Soc Trop Med Hyg 2000;94:549-53.
63. Greenwood B. Review: Intermittent preventive treatment—a new approach to the prevention of malaria in children in areas with seasonal malaria transmission. Trop Med Int Health 2006;11:983-91.
64. Shetty AK, Woods CR. Prevention of malaria in children. Pediatr Infect Dis J 2006;25:1173-6.
65. O'Meara WP, Breman JG, McKenzie FE. The promise and potential challenges of intermittent preventive treatment for malaria in infants (IPTi). Malar J 2005;4:33.
66. WHO. Taking Stock: HIV in children. Geneva: WHO; 2006 [cited 2007 May 2]. Available from: http://www.who.int/hiv/pub/advocacy/children/en/.
67. Spira R, Lepage P, Msellati P, Van De Perre P, Leroy V, Simonon A, et al. Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda. Mother-to-Child HIV-1 Transmission Study Group. Pediatrics 1999;104:e56.
68. Taha TE, Graham SM, Kumwenda NI, Broadhead RL, Hoover DR, Markakis D, et al. Morbidity among human immunodeficiency virus-1-infected and -uninfected African children. Pediatrics 2000;106:e77.

69. Walker N, Schwartlander B, Bryce J. Meeting international goals in child survival and HIV/AIDS. Lancet 2002;360: 284-9.
70. UNICEF. HIV/AIDS: Preventing Mother to Child Transmission [updated 2006 March; cited 2007 June 20]. Available from: http://childinfo.org/areas/hivaids/mtct.php.
71. De Cock KM, Fowler MG, Mercier E, de Vincenzi I, Saba J, Hoff E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. JAMA 2000;283:1175-82.
72. Brocklehurst P, Volmink J. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev 2002(1):CD003510.
73. Coovadia HM, Rollins NC, Bland RM, Little K, Coutsoudis A, Bennish ML, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. Lancet 2007;369: 1107-16.
74. Thior I, Lockman S, Smeaton LM, Shapiro RL, Wester C, Heymann SJ, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. JAMA 2006;296:794-805.
75. Iliff PJ, Piwoz EG, Tavengwa NV, Zunguza CD, Marinda ET, Nathoo KJ, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. AIDS 2005;19:699-708.
76. WHO. WHO HIV and Infant Feeding Technical Consultation. Consensus Statement. Held on behalf of the Interagency Task Team (IATT) on Prevention of HIV Infections in Pregnant Women, Mothers and their Infants. Geneva, 2006 [cited 2007 May 24]. Available from: http://www.who.int/child-adolescent-health/publications/NUTRITION/consensus_statement.htm.
77. Kline MW. Perspectives on the pediatric HIV/AIDS pandemic: catalyzing access of children to care and treatment. Pediatrics 2006;117:1388-93.
78. Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. Int J Tuberc Lung Dis 2004;8:636-47.
79. Stop TB Partnership Childhood TB Subgroup World Health Organization. Guidance for National Tuberculosis Programmes on the management of tuberculosis in children. Chapter 1: introduction and diagnosis of tuberculosis in children. Int J Tuberc Lung Dis 2006;10:1091-7.
80. Nelson LJ, Wells CD. Tuberculosis in children: considerations for children from developing countries. Semin Pediatr Infect Dis 2004;15:150-4.
81. Enarson PM, Enarson DA, Gie R. Management of tuberculosis in children in low-income countries. Int J Tuberc Lung Dis 2005;9:1299-304.
82. Grange JM, Zumla A. Tuberculosis. In: Cook GC, Zumla A, editors. Manson's Tropical Diseases. 21st Edition. London: Elsevier Science; 2003. p. 995-1052.
83. Adams LV. Childhood tuberculosis in the developing world. Pediatr Ann 2004;33:685-90.
84. Colditz GA, Berkey CS, Mosteller F, Brewer TF, Wilson ME, Burdick E, et al. The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. Pediatrics 1995;96(1 Pt. 1):29-35.
85. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 2006;367:1173-80.
86. WHO. TB/HIV. A Clinical Manual. 2nd Edition. Geneva: WHO; 2004 [cited 2007 May 2]. Available from: http://www.who.int/tb/publications/who_htm_tb_2004_329/en/index.html.
87. Neumann CG, Gewa C, Bwibo NO. Child nutrition in developing countries. Pediatr Ann 2004;33:658-74.
88. Muller O, Krawinkel M. Malnutrition and health in developing countries. CMAJ 2005;173:279-86.
89. Collins S, Dent N, Binns P, Bahwere P, Sadler K, Hallam A. Management of severe acute malnutrition in children. Lancet 2006;368:1992-2000.
90. Caulfield LE, Richard SA, Rivera JA, Musgrove P, Black RE. Stunting, wasting, and micronutrient deficiency disorders. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al, editors. Disease control priorities in developing countries. 2nd Edition. New York: Oxford University Press; 2006. p. 551-67 [cited 2007 May 10]. Available from: http://www.dcp2.org/pubs/DCP.
91. Bhan MK, Bhandari N, Bahl R. Management of the severely malnourished child: perspective from developing countries. BMJ 2003;326:146-51.
92. UNICEF. The 2006 State of the World's Children. Excluded and Invisible. New York: UNICEF, 2006 [cited 2007 March 28]. Available from: http://www.unicef.org/sowc06/.
93. Rice AL, Sacco L, Hyder A, Black RE. Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. Bull World Health Organ 2000;78:1207-21.
94. Bahl R, Frost C, Kirkwood BR, Edmond K, Martines J, Bhandari N, et al. Infant feeding patterns and risks of death and hospitalization in the first half of infancy: multicentre cohort study. Bull World Health Organ 2005;83:418-26.
95. WHO. Complementary feeding: Report of the global consultation convened jointly by the Department of Child and Adolescent Health and Development and the Department of Nutrition for Health and Development, Geneva, 10-13 December 2001 and Summary of guiding principles for complementary feeding of the breastfed child. Geneva: WHO; 2002 [cited 2007 June 20]. Available from: http://www.who.int/child-adolescent-health/publications/NUTRITION/Report_CF.htm.
96. Nestel P, Briend A, de Benoist B, Decker E, Ferguson E, Fontaine O, et al. Complementary food supplements to achieve micronutrient adequacy for infants and young children. J Pediatr Gastroenterol Nutr 2003;36:316-28.
97. Bhutta ZA. Effect of infections and environmental factors on growth and nutritional status in developing countries. J Pediatr Gastroenterol Nutr 2006;43(Suppl 3):S13-21.
98. UNICEF. Progress for children: a report card on nutrition. Number 4, May, 2006. New York: UNICEF, 2006 [cited 2007 June 15]. Available from: http://www.unicef.org/progressforchildren/2006n4/index.html.
99. West KP Jr. Vitamin A deficiency disorders in children and women. Food Nutr Bull 2003;24(Suppl 4):S78-90.

100. Ramakrishnan U, Aburto N, McCabe G, Martorell R. Multimicronutrient interventions but not vitamin a or iron interventions alone improve child growth: results of 3 meta-analyses. J Nutr 2004;134:2592-602.
101. Beaton GH, Martorell R, Aronson KA, Edmonston B, McCabe G, Ross AC, et al. Vitamin A supplementation and child morbidity and mortality in developing countries. Food Nutr Bull 1993/1994;15 [cited 2007 June 15]. Available from: http://www.unu.edu/unupress/food/8F154e/8F154E00.htm.
102. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality. A meta-analysis. JAMA 1993;269:898-903.
103. UNICEF. UNICEF Statistics: Vitamin A Deficiency [updated 2006 May; cited 2007 June 20]. Available from: http://childinfo.org/areas/vitamina/.
104. Huiming Y, Chaomin W, Meng M. Vitamin A for treating measles in children. Cochrane Database Syst Rev 2005(4): CD001479.
105. Brown N, Roberts C. Vitamin A for acute respiratory infection in developing countries: a meta-analysis. Acta Paediatr 2004;93:1437-42.
106. Ross, DA. Recommendations for vitamin A supplementation. J Nutr 2002;132(Suppl 9):S2902-6.
107. Maberly GF, Haxton DP, van der Haar F. Iodine deficiency: consequences and progress toward elimination. Food Nutr Bull 2003;24(Suppl 4):S91-8.
108. WHO. Iodine Status Worldwide. WHO Global Database on Iodine Deficiency. Geneva: World Health Organization, 2004 [cited 2007 May 26]. Available from: http://whqlibdoc.who.int/publications/2004/9241592001.pdf.
109. Bhatnagar S, Natchu UC. Zinc in child health and disease. Indian J Pediatr 2004;71:991-5.
110. Shrimpton R, Gross R, Darnton-Hill I, Young M. Zinc deficiency: what are the most appropriate interventions? BMJ 2005;330:347-9.
111. Black MM. Micronutrient deficiencies and cognitive functioning. J Nutr 2003;133(11 Suppl 2):S3927-31.
112. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. J Pediatr 1999;135:689-97.
113. Black RE. Zinc deficiency, infectious disease and mortality in the developing world. J Nutr 2003;133(5 Suppl 1): S1485-9.
114. Bhutta ZA, Bird SM, Black RE, Brown KH, Gardner JM, Hidayat A, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 2000;72:1516-22.
115. Brooks WA, Yunus M, Santosham M, Wahed MA, Nahar K, Yeasmin S, et al. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. Lancet 2004; 363:1683-8.
116. Thacher TD, Fischer PR, Strand MA, Pettifor JM. Nutritional rickets around the world: causes and future directions. Ann Trop Paediatr 2006;26:1-16.
117. Stoltzfus RJ. Iron deficiency: global prevalence and consequences. Food Nutr Bull 2003;24(Suppl 4):S99-103.
118. Ronsmans C, Graham WJ. Maternal mortality: who, when, where, and why. Lancet 2006;368:1189-200.
119. Mannar MG. Successful food-based programmes, supplementation and fortification. J Pediatr Gastroenterol Nutr. 2006;43(Suppl 3):S47-53.
120. Zlotkin SH, Schauer C, Christofides A, Sharieff W, Tondeur MC, Hyder SM. Micronutrient sprinkles to control childhood anaemia. PLoS Med 2005;2:e1.
121. Smuts CM, Lombard CJ, Benade AJ, Dhansay MA, Berger J, Hop le T, et al. Efficacy of a foodlet-based multiple micronutrient supplement for preventing growth faltering, anemia, and micronutrient deficiency of infants: the four country IRIS trial pooled data analysis. J Nutr 2005;135:S631-8.
122. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich Sachs S, Sachs JD. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med 2006;3:e102.
123. Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet 2006;367:1521-32.
124. Hotez PJ, Bundy DAP, Beegle K, Brooker LD, de Silva N, Montresor A, et al. Helminth infections: soil-transmitted helminth infections and schistosomiasis. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al, editors. Disease control priorities in developing countries. 2nd edition. New York: Oxford University Press; 2006. p. 467-482 [cited 2007 May 26]. Available from: http://www.dcp2.org/pubs/DCP.
125. Gilles HM. Soil-transmitted Helminths (Geohelminths). In: Cook GC, Zumla A, editors. Manson's tropical diseases. 21st edition. London: Elsevier Science, 2003. p. 1527-60.
126. Gryseels B, Polman K, Clerinx J, Kestens L. Schistosomiasis. Lancet 2006;368:1106-18.
127. WHO. Prevention and Control of Schistosomiasis and Soil Transmitted Helminths. Geneva; WHO: 2002 [cited 2007 April 27]. Available from: http://www.who.int/wormcontrol/documents/joint_statements/en/ppc_unicef_finalreport.pdf.
128. World Health Organization (WHO). Schistosomiasis and soil-transmitted helminth infections – preliminary estimates of the number of children treated with albendazole or mebendazole. Wkly Epidemiolog Rec 2006;15:145-64.
129. WHO. Scaling up schistosomiasis and soil-transmitted helminthiasis control. Report from meeting of Members of the Partners for Parasite Control, 14-15 December 2006. Geneva: WHO; 2006 [cited 2007 June 20]. Available from: http://www.who.int/neglected_diseases/scalingup/en/index.html.
130. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. Lancet 2007; 369:60-70.
131. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, et al. Child development: risk factors for adverse outcomes in developing countries. Lancet 2007; 369:145-57.
132. Engle PL, Black MM, Behrman JR, Cabral de Mello M, Gertler PJ, Kapiriri L, et al. Strategies to avoid the loss of

developmental potential in more than 200 million children in the developing world. Lancet 2007;369:229-42.
133. Olness K. Effects on brain development leading to cognitive impairment: a worldwide epidemic. J Dev Behav Pediatr 2003;24:120-30.
134. Galler JR, Ramsey FC, Forde V, Salt P, Archer E. Long-term effects of early kwashiorkor compared with marasmus. II. Intellectual performance. J Pediatr Gastroenterol Nutr 1987; 6:847-54.
135. Grantham-McGregor SM, Powell CA, Walker SP, Himes JH. Nutritional supplementation, psychosocial stimulation, and mental development of stunted children: the Jamaican Study. Lancet 1991;338:1-5.
136. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001;131:S649-66.
137. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. Arch Pediatr Adolesc Med 2006;160:1108-13.
138. Iannotti LL, Tielsch JM, Black MM, Black RE. Iron supplementation in early childhood: health benefits and risks. Am J Clin Nutr 2006;84:1261-76.
139. Boivin MJ, Bangirana P, Byarugaba J, Opoka RO, Idro R, Jurek AM, et al. Cognitive impairment after cerebral malaria in children: a prospective study. Pediatrics 2007;119:e360-6.
140. Olusanya BO, Newton VE. Global burden of childhood hearing impairment and disease control priorities for developing countries. Lancet 2007;369:1314-7.
141. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? Lancet 2005;365:891-900.
142. Lawn JEZJ, Begkoyian G, Knippenberg R. Newborn survival. In: Dean JTBJG, Measham AR, Alleyne G, Claeson M, Evans DB, et al, editors. Disease control priorities in developing countries. 2nd Edition. New York: Oxford University Press, 2006. p. 531-49 [cited 2007 May 26]. Available from: http://www.dcp2.org/pubs/DCP.
143. Knippenberg R, Lawn JE, Darmstadt GL, Begkoyian G, Fogstad H, Walelign N, et al. Systematic scaling up of neonatal care in countries. Lancet 2005;365:1087-98.
144. Martines J, Paul VK, Bhutta ZA, Koblinsky M, Soucat A, Walker N, et al. Neonatal survival: a call for action. Lancet 2005;365:1189-97.
145. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066-74.
146. Stanton C, Lawn JE, Rahman H, Wilczynska-Ketende K, Hill K. Stillbirth rates: delivering estimates in 190 countries. Lancet 2006;367:1487-94.
147. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS. How many child deaths can we prevent this year? Lancet 2003;362:65-71.
148. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet 2000;355:451-5.
149. Caulfield LE, Huffman SL, Piwoz EG. Interventions to improve intake of complementary foods by infants 6 to 12 months of age in developing countries: impact on growth and on the prevalence of malnutrition and potential contribution to child survival. Food Nutr Bull 1999;20:183-200.
150. Fewtrell L, Kaufmann RB, Kay D, Enanoria W, Haller L, Colford JM Jr. Water, sanitation, and hygiene interventions to reduce diarrhoea in less developed countries: a systematic review and meta-analysis. Lancet Infect Dis 2005;5:42-52.
151. Esrey SA, Potash JB, Roberts L, Shiff C. Effects of improved water supply and sanitation on ascariasis, diarrhoea, dracunculiasis, hookworm infection, schistosomiasis, and trachoma. Bull World Health Organ 1991;69:609-21.
152. Luby SP, Agboatwalla M, Feikin DR, Painter J, Billhimer W, Altaf A, et al. Effect of handwashing on child health: a randomised controlled trial. Lancet 2005;366:225-33.
153. Victora CG, Adam T, Bryce J, Evans DB. Integrated management of the sick child. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al, editors. Disease control priorities in developing countries. 2nd Edition. New York: Oxford University Press; 2006. p. 1177-91 [cited 2007 May 26]. Available from: http://www.dcp2.org/pubs/DCP.
154. WHO. Handbook: IMCI integrated management of childhood illness. Geneva: WHO; 2005 [cited 2007 May 19]. Available from: http://www.who.int/child-adolescent-health/New_Publications/IMCI/WHO_FCH_CAH_00.12/IMCI_Handbook.pdf.
155. Armstrong Schellenberg J, Bryce J, de Savigny D, Lambrechts T, Mbuya C, Mgalula L, et al. The effect of Integrated Management of Childhood Illness on observed quality of care of under-fives in rural Tanzania. Health Policy Plan 2004;19:1-10.
156. Armstrong Schellenberg JR, Adam T, Mshinda H, Masanja H, Kabadi G, Mukasa O, et al. Effectiveness and cost of facility-based Integrated Management of Childhood Illness (IMCI) in Tanzania. Lancet 2004;364:1583-94.
157. Huicho L, Davila M, Gonzales F, Drasbek C, Bryce J, Victora CG. Implementation of the Integrated Management of Childhood Illness strategy in Peru and its association with health indicators: an ecological analysis. Health Policy Plan 2005;20(Suppl 1):i32-41.
158. El Arifeen S, Blum LS, Hoque DM, Chowdury EK, Khan R, Black RE, et al. Integrated Management of Childhood Illness (IMCI) in Bangladesh: early findings from a cluster-randomised study. Lancet 2004;364:1595-602.
159. Bryce J, Victora CG, Habicht JP, Vaughan JP, Black RE. The multi-country evaluation of the integrated management of childhood illness strategy: lessons for the evaluation of public health interventions. Am J Public Health 2004;94: 406-15.
160. Bryce J, Terreri N, Victora CG, Mason E, Daelmans B, Bhutta ZA, et al. Countdown to 2015: tracking intervention coverage for child survival. Lancet 2006;368:1067-76.
161. Claeson M, Gillespie D, Mshinda H, Troedsson H, Victora CG. Knowledge into action for child survival. Lancet 2003; 362:323-7.
162. Victora CG, Fenn B, Bryce J, Kirkwood BR. Co-coverage of preventive interventions and implications for child-survival

strategies: evidence from national surveys. Lancet 2005; 366:1460-6.
163. Fotso JC. Child health inequities in developing countries: differences across urban and rural areas. Int J Equity Health 2006;5:9.
164. Schellenberg JA, Victora CG, Mushi A, de Savigny D, Schellenberg D, Mshinda H, et al. Inequities among the very poor: health care for children in rural southern Tanzania. Lancet 2003;361:561-6.
165. Wirth ME, Balk D, Delamonica E, Storeygard A, Sacks E, Minujin A. Setting the stage for equity-sensitive monitoring of the maternal and child health millennium development goals. Bull World Health Organ 2006;84:519-27.
166. Victora CG, Huicho L, Amaral JJ, Armstrong-Schellenberg J, Manzi F, Mason E, et al. Are health interventions implemented where they are most needed? District uptake of the integrated management of childhood illness strategy in Brazil, Peru and the United Republic of Tanzania. Bull World Health Organ 2006;84:792-801.