Childhood Diarrhea in Sub-Saharan Africa

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Foreword

Diarrheal disease remains a leading cause of mortality and morbidity of children in Sub-Saharan Africa, a region where unique geographic, economic, political, sociocultural, and personal factors interact to create distinctive continuing challenges to its prevention and control. Whereas childhood mortality rates from diarrhea are expected to decrease by 30 to 50% in most areas of the world between 1990 and 2000, the decline in Sub-Saharan Africa is estimated to be only 3%.* Consequently, approximately 40% of childhood deaths from diarrhea worldwide will occur in Sub-Saharan Africa by the year 2000, although only 19% of the world's population under the age of five years will live in this region.* This continuing epidemic deserves sustained programmatic and research attention as international public health moves on to confront newer issues in infectious disease and the changing burdens of disease associated with the demographic transition.

A number of different social, political, and economic factors are present in Sub-Saharan Africa which contribute to the constant morbidity from acute and persistent diarrhea, as well as intermittent epidemics of cholera and dysentery common to this region of the world. Morbidity and mortality from childhood diarrhea, whether due to invasive enteropathogens such as *Shigella* or the more commonplace rotavirus, are further compounded by inappropriate household case management and the frequent misuse of antibiotics. Limited knowledge among many health care providers of the proper treatment of diarrhea also contributes to poor outcomes. The overuse of antimicrobials exerts a selective pressure for the development of antimicrobial resistance throughout the continent. Antimicrobial resistance will increasingly limit a practitioner's ability to successfully manage cholera and dysenteric diarrheas.

This report on childhood diarrhea in Sub-Saharan Africa is intended to provide an overview of the current state of this problem and to highlight key areas for future research. Given the continued importance of diarrheal disease as a major contributor to childhood morbidity and mortality in Africa, there is a clear need for vigorous efforts to implement the new Integrated Management of Childhood Illness (IMCI) approach to improve diarrhea case management. There is also an urgent need to develop interventions to limit the spread of antimicrobial resistance among bacterial enteropathogens.

Davidson H. Hamer, M.D.
ARCH Project Scientist

Jonathon Simon, M.P.H.
ARCH Project Director

Donald Thea, M.D., M.Sc.
ARCH Project Scientist

Gerald T. Keusch, M.D.
ARCH Scientific Director

* *The Global Burden of Disease*, CJC Murray & AD Lopez. 1996

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Methods

To compile information on diarrhea in Sub-Saharan Africa, we performed a computer search of the scientific literature in the MEDLINE database from 1966 through 1997. In addition, we reviewed the bibliographies of relevant articles. A total of 298 papers were reviewed from these two sources, but many were not included in the preparation of this review because they were of insufficient scope or quality (see below).

The difficulties encountered in designing and implementing prospective, community-based studies of diarrhea in Africa are numerous. Recruitment obstacles may arise from caretaker fears, cultural beliefs, and a lack of family or tribal consent. Longitudinal surveillance may be hindered by inefficient telecommunications, poor public transportation, wide dispersion of rural communities, low population density, inconsistent house-numbering schemes, incomplete mapping and census information, mobility of the study population, and inadequate incentives for participation. The capacity to design and carry out clinical trials is typically limited in the very regions where research is desperately needed. Despite the numerous obstacles to the implementation of well-designed clinical research in Sub-Saharan Africa, considerable information on many aspects of diarrheal disease has accumulated during the last two decades.

Prospective community-based studies of diarrheal mortality were selected for inclusion in this review if surveillance was done at least monthly. Morbidity data were derived from prospective studies with frequent active surveillance (at least monthly) which also included a clearly stated definition of diarrhea. Though we are aware of the potential limitations of monthly recall data, there were insufficient surveillance data using more frequent recall periods. Data from cross-sectional survey studies were included if relevant longitudinal data were unavailable. Outcomes evaluated included the incidence (number of episodes/child/time period), and prevalence (proportion of children with diarrhea at one point in time) of diarrhea, episode duration, and cumulative time spent with diarrhea. Only cross-sectional and prospective studies that provided clear definitions of diarrheal episodes and nutritional status were included in the evaluation of the relationship of nutritional status and diarrhea.

Studies of specific pathogens responsible for acute or persistent diarrhea were included if they contained a clear definition of diarrhea, non-diarrheic controls, and an adequate description of microbiological methods. Because the number of prospective studies of diarrhea etiologies is limited, cross-sectional studies that met these criteria were also included. Studies of risk factors for acute or persistent diarrhea were reviewed if they contained appropriately matched controls. Studies that did not define diarrhea or did not contain an adequate control group are discussed only if they are the sole identified source of information on a specific subject. Differences in the definition of diarrhea, the type of population studied, selection of appropriate controls, presence of recall bias, and study design may be responsible for the conflicting findings seen in studies of the determinants of disease.

Burden of Disease from Diarrhea in Sub-Saharan Africa

Mortality

Diarrhea is one of the top three causes of childhood mortality in Sub-Saharan Africa, estimated from community-based surveys or vital statistics registries and census data. A comprehensive review of worldwide diarrheal mortality data derived from prospective, community-based studies of stable populations with low migration rates lasting at least one year showed that only three studies in Africa met these strict selection criteria, all of which were limited to children less than four years old [1]. Overall death rates ranged from 3.6 to 24 per 1,000 population in these three studies. This review was updated a decade later using studies that reported age-specific mortality data, and information from longitudinal and cross-sectional studies as well as vital registries [2]. The more recent data showed that childhood mortality rates from diarrhea in Africa remained high; the rates were similar to those found in South Asian studies and were consistently higher than in Latin America. In contrast, analysis of survey data from national diarrheal disease control programs revealed a decrease in the median number of

deaths per 1000 population in children under five years old, from 11.8 in the period from 1982 to 1984 to 5.1 in 1987 - 90[2]. Our compilation of data from prospective, community-based studies found that acute diarrhea-associated mortality rates ranged from 3.4 to 31 per 1000 children per year (Table 1). Acute diarrhea accounted for 1.9 to 37% of all deaths, with the greatest proportion of deaths from acute diarrhea usually occurring in the first year of life. Persistent diarrhea (duration more than 14 days) is also responsible for significant childhood mortality in Sub-Saharan Africa, where rates of 6.6 to 43 deaths/1000 children/year have been observed (Table 1)[3-5].

Table 1. Mortality from acute and persistent diarrhea in Sub-Saharan Africa

Country	Author(s)	Period of study	Study locale	Frequency of visits	Age (years) children	Mortality rate (deaths per 1000 per year)
The Gambia	Marsden[34]	1960-62	Sukuta (semi-rural)	Weekly	0-1.5	19.4 (1.9% of deaths due to diarrhea)
The Gambia	Greenwood et.al[173]	1982-83 1986-87	Farafenni (rural)	Monthly	<5	4.8[a]/6.6[b]; 9.2[a]/6.7[b]
Guinea-Bissau	Molbak et al.[4]	1987-90	Bandim II (semi-urban)	Weekly	<5	31[a]/43[c]; 14%[a]/16%[c] of deaths due to diarrhea
Kenya	Omondi-Odhiambo et al.[6]	1975-78	Machakos (rural)	Biweekly	<5	3.4
Malawi	Lindskog[182]	1983-88 1984-85	Chingale (rural)	Biweekly	<5	18.0
Nigeria	Bradley and Gilles[16]	1977-78	Malumfash I (rural)	Monthly	All	37% of children <4 yrs died from diarrhea
Nigeria	Rea[22]	1960s 2-year duration	Lagos (urban)	Every 2 to 3 weeks	<5	24
Sudan	Woodruff et al.[183]	NA	Juba (urban)	Monthly	<1	7.9% died from diarrhea
Tanzania	Mtango and Neuvians[172]	1984-85	Bagamoyo (rural)	Every 6 to 8 weeks	<5	5.6; 14% of deaths due to diarrhea
Dem. Rep. of the Congo	Thea[5]	1989-90	Kinshasa (urban)	Monthly	<1	12[d]; 31% of deaths due to diarrhea

a: Acute diarrhea
b: Chronic diarrhea and malnutrition
c: Persistent diarrhea and malnutrition
d: HIV-seronegative infants

Mortality rates are significantly increased in the presence of HIV infection as evidenced by a well-designed and implemented study with monthly surveillance of HIV-seropositive and seronegative infants in an urban area of the Democratic Republic of the Congo (formerly Zaire)[5]. The diarrhea-attributable mortality of 12.0 deaths per 1000 live births in the HIV-negative cohort increased to 132 deaths/1000 live births in HIV-positive infants. Much of this increase was due to a rise in deaths associated with persistent diarrhea.

The case-fatality rate among children with less severe disease reported in a community-based study in Kenya involved only 0.1% of all episodes of diarrhea[6], whereas rates among children requiring hospitalization for diarrhea ranged from 9.4 to 19%[7-10]. Persistent diarrhea, acute dehydration, malnutrition, sepsis, underlying HIV infection, measles, and complications of invasive diarrhea all increase the likelihood of death from diarrhea[3,5,9]. Multivariate analyses of predictors of fatal diarrheal episodes in two case-control studies of hospitalized children less than five years old from Lesotho found that illness duration of seven or more days before hospitalization, age less than six months, and the presence of a major concurrent infection (measles, pneumonia, meningitis, or sepsis) were all independently associated with death[9]. During the postneonatal period infants are at the greatest risk of lethal diarrheal disease[1,2,6,11-14]. Thereafter, death rates from diarrhea decline with age; however, only limited data are available regarding death rates in children over five years old[14,15].

Persistent or recurrent diarrhea (two or more episodes separated by at least three days of normal stool output) are important risk factors for mortality in neonates and infants[4,5]. Higher mortality rates from diarrhea have been observed in some countries or regions during the wet season[3,16,17] or among families with lower socioeconomic status, or poor hygiene practices[18].

Morbidity

The median annual incidence of diarrhea in Sub-Saharan Africa peaks among infants 6 to 12 months old and decreases progressively thereafter[13,19-24]. Most incidence studies have restricted their focus to children less than five years old, and data for older children are limited to one cross-sectional survey from Imo State, Nigeria[25]. A review of longitudinal community-based studies with frequent surveillance found that 6- to 11-month-old children in Africa had a median of 4.5 diarrhea episodes per year[2]. This rate was higher than that found in many Asian studies but was lower than in Latin America. However, a number of the morbidity studies from Latin America which were carried out during the 1980s used more frequent surveillance, which may yield higher incidence rates[2]. The median yearly incidence rates of diarrhea in Africa and Latin America are nearly identical if the Latin American studies with more frequent (twice weekly) surveillance are excluded. A comprehensive analysis of 73 studies from 23 countries during 1970 to 1990 found that children under five years of age in Sub-Saharan Africa experience about five episodes of diarrhea yearly (range of 1.6 to 9.9)[11]. Prospective studies of the incidence of diarrhea that covered at least a one-year interval reported a range of 1.0 to 7.3 episodes/child/year (Table 2). Pooling all studies, including those limited to the rainy season, shows a prevalence of diarrhea in children of 10.5 to 19%. Unlike the decline in mortality rates, diarrhea incidence does not appear to have changed substantially over the last decade[1,2].

Diarrhea has been estimated to be responsible for 25 to 75% of all childhood illnesses in Africa[11,25,26]. Episodes of diarrhea lead to about 14% of outpatient visits, 16% of hospital admissions, and account for an average of 35 days of illness per year in children less than five years old[11].

A limited number of prospective studies in Sub-Saharan Africa have found that persistent diarrhea accounts for 2.4 to 11.4% of all diarrhea episodes[27,31] but 22% of the total days of diarrhea recorded in a rural cohort in Zimbabwe[29]. Although the definition of a new episode was similar (two to three or more diarrhea-free days between attacks), only three of these studies extended over at least a full year to eliminate the effect of seasonal variation on diarrheal incidence[29-31]. This may account, in part, for the lowest incidence, (2.4%), which was observed in the study with the shortest duration[27]. Thea et al. found four episodes of persistent diarrhea per 100 child-years of observation in

Table 2: Morbidity from acute diarrhea in Sub-Saharan Africa

Country	Author(s)	Study duration (months)	Study locale	Frequency of visits	Age (years)	Morbidity
Ethiopia	Freij and Wall[13]	12	Addis Ababa (urban)	Biweekly	0-12	0-23 mo[1]: median 6.6 episodes/yr (63 days/yr) 5-12 yr: median 1.0 (4 days/yr)
The Gambia	Goh Rowland et al.[31]	24	Bakau (urban)	Weekly	0-2	7.3 episodes/child/yr
The Gambia	Rowland et. al.[38]	24	Bakau (urban)	Weekly	0-2	18.7% prevalence
The Gambia	Pickering et al.[184]	4	Bakau (urban)	Weekly	0.5-3	12.0% prevalence (2.8 episodes/child)
Ghana	Biritwum et al.[19]	12	Gomoa Fettah (rural)	Weekly	0-6	1.9 episodes/child/yr
Guinea-Bissau	Molbak et al.[62]	12	Bandim II (urban)	Weekly	<3	13% prevalence (2.6 episodes/100 days at risk)
Kenya	Leeuwenburg et al.[23]	36	Machakos (rural)	Biweekly	<5	2.2% average 2-weekly incidence
Nigeria	Tomkins[44]	3	Malumfashi (rural)	Weekly	<3	1.4 episodes/child/3mo (10.5% of time spent with diarrhea)
Nigeria	Huttly et al.[175]	48	Imo State (rural)	Biweekly	<6	1983: 4.1-6.7 episodes/child/yr 1986: 2.5-2.9 episodes/child/yr[7]
Dem. Rep. of the Congo	Haggerty et al.[28]	3	Bandundu	Weekly	<3	1.9 episodes/child/3 mo (11% of time spent with diarrhea)
D.R.O.C.	Thea et al.[5]	16	Kinshasa (urban)	Monthly from birth to 12 months then bimonthly	<2	100 episodes/ 100 child-yrs[8]
Zimbabwe	Moy et al.[29]	22	Shamva (rural)	Weekly	<2	13-18 month age range (3 episodes/6 mo)

1. Morbidity measures are for gastroenteritis, which was defined as the presence of vomiting and/or diarrhea. Diarrhea was defined as at least four loose or one watery stool in a 24-hour period.
2. Maternal definition of diarrhea.
3. The mother's opinion of whether a stool was diarrheal was verified by study investigator who agreed in the majority of cases.
4. Study done during the rainy season in which the highest incidence of diarrhea is usually found in this region.
5. Diarrhea was defined as three or more loose stools in a 23-hour period.
6. Field workers evaluated children's stools to determine if they had diarrhea.
7. Control villages only. 1983 data are for both control and intervention villages.
8. Data are for HIV-negative children only.

an HIV-seronegative birth cohort in Dem. Rep. of the Congo[5]. This incidence rate is substantially lower than that reported in other parts of the developing world[32], however these children were all receiving frequent basic primary health care as part of an ongoing study of perinatal transmission of HIV. Differences in the frequency of surveillance and type of community studied also contribute to the wide regional variations in the incidence of persistent diarrhea.

Causes of Diarrheal Diseases in Sub-Saharan Africa

Malnutrition

Acute and chronic infections contribute to malnutrition by causing decreased food intake, impaired absorption, increased losses of fluid, electrolytes, protein, and iron, and by altering the normal metabolism[33]. Evidence from numerous studies of children under five years of age in developing countries suggests that both acute and persistent episodes of diarrhea predispose to or exacerbate malnutrition[34,35,36], and conversely chronic malnutrition may be a risk factor for diarrhea[37]. Data from Sub-Saharan Africa illustrate the complex interaction between diarrhea and malnutrition that has been found in other developing regions of the world. Differences in measurement tools and the timing of nutritional assessments among studies may explain some of the variance in the reported results.

Prospective, community-based studies in The Gambia, Uganda, and Sudan indicate that diarrheal disease leads to impaired weight gain[33,38-42]. The impact of diarrhea on weight gain was greatest in 7- to 12-month-old infants and was fourfold higher among weaned than exclusively breast-fed children[38]. A notable exception was a study in rural Zimbabwe, which failed to find a significant adverse effect of acute diarrhea on weight gain[43]. Although growth faltering was severe during and immediately after an episode of diarrhea, the return to a child's previous growth curve was 90% complete within a month. Moreover, children with frequent diarrhea episodes had similar growth rates when compared to those with infrequent episodes. However, since both cases and controls showed mean weight and height which were only in the third percentile of the National Center for Health Statistics (NCHS) standards, inadequate dietary intake in this economically deprived population is an obvious confounding variable.

Pre-existing malnutrition also increased the likelihood of diarrheal disease. Decreased weight-for-age was significantly associated with an increased incidence or prevalence of diarrhea in all studies but one[43] (Table 3). Diminished height-for-age or stunting, generally accepted as an indication of chronic undernutrition, was associated with a significantly increased risk of diarrhea in two studies[19,45] but not in another[44]. A significant association between decreased weight-for-height and diarrhea rates was observed in two of these studies[19,44] but not in the third[45]. A cross-sectional study of acute diarrhea in a rural community in the Sudan also demonstrated a significant association between low weight-for-age (<75%) and diarrhea, with an apparent dose-response relationship[46]. Furthermore, the duration of a diarrheal episode was increased in underweight, wasted, and stunted Nigerian children[44]. In two studies the effect of malnutrition on the risk of diarrhea remained after adjustment for age, water availability and quality, personal hygiene practices, and family income[45,46]. Similar findings have been reported from Bangladesh[47,48] although these failed to show an increased incidence of diarrhea in malnourished children.

Severe vitamin A deficiency (manifested by xerophthalmia) was shown to be associated with an increased risk of diarrheal disease among children in Asia[49] and Ethiopia[50], while low dietary intake of vitamin A was a risk factor for diarrhea in Sudanese children[32]. Neither African study, however, controlled for the possible confounding effect of nutritional status on the incidence of diarrhea.

A meta-analysis of randomized trials of vitamin A supplementation performed worldwide found a 39% reduction in mortality due to diarrheal disease in vitamin A supplemented children[52]. Similar promising findings have been obtained in studies in Sub-Saharan Africa. In two carefully designed and implemented, placebo-controlled studies in Ghana, vitamin A supplementation for non-xeroph-

Table 3. Effects of nutritional state on the frequency of diarrhea in prospective studies of African children.

Author(s)	Year of study	Country	Study location/	Weight-for-age (cut-off level) duration	Height-for-age (cutt-off)	Weight-for height (<80%)
Freij Wall[13]	1972-73	Ethiopia	Urban/ 1 year	Increased (<80%ile)	Not studied	Not studied
Tomkins[44]	1979	Nigeria	Rural/ 3 months	No effect (<75%ile)	No effect (<90%ile)	Increased
Biritwum[19]	1982	Ghana	Rural/ 1 year	Increased (<80%ile)	Increased (<90%ile)	Increased
Tomkins[45]	1981	The Gambia	Urban/ two 3 mo periods	Increased (<-2SD)	Increased (<-3SD)	Increased

thalmic children was associated with a 19% reduction in mortality from acute diarrhea, and evidence of reduced diarrhea morbidity as well[53,54]. The effect of supplementation was greatest on the incidence of severe dehydrating diarrhea, and the frequency of clinic attendance, or hospital admissions. A comparison of vitamin A and E supplementation in the Sudan demonstrated no difference in the decrease in diarrhea-associated mortality in either group[55]. Another study of a combined vitamin A and E supplement versus a vitamin E control in South Africa given at months 1, 3, 6, and 9 did not have sufficient power to evaluate the effect of the micronutrient supplement on mortality[56]. However, there was a significant reduction in diarrhea overall as well as a trend toward a reduction in hospitalization for diarrhea and the number of episodes lasting more than seven days in the vitamin A-supplemented group. Differences in study population characteristics, the dosage and the frequency of vitamin A supplementation may account for these discrepant findings. The choice of vitamin E for placebo may be inappropriate given the growing evidence that vitamin E may have beneficial effects on the immune system with a resultant reduction in the incidence of infections[57].

The role of zinc supplementation for the treatment and/or prevention of diarrheal disease has been evaluated in Sub-Saharan Africa on a very limited basis. A placebo-controlled trial in The Gambia of a high dose zinc gluconate supplement administered twice weekly was designed primarily to evaluate the effect of zinc on the growth of children in a rural community[58]. This study found that zinc supplementation failed to reduce the number of clinic visits for diarrheal disease. Nevertheless, this research provided interesting results that have served to generate new hypotheses on the role of zinc as an adjunct to the therapy or prevention of childhood infectious diseases.

Pathogens

Controlled prospective and cross-sectional studies of children with acute diarrhea presenting to outpatient medical facilities or admitted to the hospital in Sub-Saharan Africa typically identify (in decreasing order of frequency) rotavirus[59,60 31,61-65]; *C. jejuni*[31,60-62,65,66]; enterotoxigenic *E. coli* (ETEC)[31,59-62,66]; enteropathogenic *E. coli* (EPEC)[60-62,65,67]; *Vibrio cholerae* 0163[61,62,66]; *Shigella*[31,60-62,65,66,67]; *Aeromonas* sp.[31,65-68]; *Salmonella* sp.[31,60-62,65-67]; *Plesiomonas shigelloides*[66,69]; *Yersinia enterocolitica*[61]; *Cryptosporidium*[62,70,71]; *Giardia lamblia*[31,59-62,66]; *Entamoeba histolytica*[59-62,66]; *Strongyloides stercoralis*[31,60,62]; and *Isospora belli*[62]. However, several of these organisms in some studies were no more prevalent in diarrheic than non-diarrheic children, for example, *C. jejuni*[31,62,65,72]. Rotavirus, ETEC, EPEC, *Shigella* sp., and *C. jejuni* were responsible for the majority of cases of acute diarrhea in Sub-Saharan Africa, as in other parts of the developing world[73,74].

Of all etiologies examined, rotavirus is most consistently found in cases than controls[31,59,60,62,63,66]. (Table 4) Data from both prospective and cross-sectional studies indicate that the incidence of rotavirus infection increases in the dry season[60,63,64,75] and is most frequent in children less than two years old, with the peak prevalence in children less than six months old[62]. An uncontrolled, prospective community-based study of diarrhea in Nigerian children found that rotavirus diarrhea peaked between three and five months of age and was often associated with dehydration[24]. As observed in other parts of the developing world[74,76] rotavirus was also associated with higher rates of dehydration than other enteric pathogens in a cross-sectional study in The Gambia[64].

A community-based prospective study of multiple potential pathogens found *Cryptosporidium*, EPEC, and rotavirus were more prevalent in cases than controls whereas ETEC, *Shigella* sp., *V. cholerae*, *Salmonella* sp., *Campylobacter* sp., and *G. lamblia* occurred with an equal or greater prevalence in asymptomatic controls[62]. This is one of a limited number of controlled studies in Sub-Saharan Africa with a clear definition of diarrhea that looked for *Cryptosporidium*, a pathogen implicated as a cause of acute and persistent childhood diarrhea in both developing and industrialized regions of the world[77]. A number of studies that failed to define diarrhea but did include asymptomatic controls have found prevalence rates of cryptosporidiosis ranging from 6 to 9% among children in Guinea Bissau, Sudan, and South Africa[78-80]. In an investigation in Democratic Republic of the Congo, *Cryptosporidium* accounted for 2% of episodes of acute diarrhea in non-HIV infected children[5]. In another study[70], there was no difference in the prevalence of cryptosporidiosis in diarrheic vs. control children but about two-thirds of the asymptomatic carriers reported diarrhea in the two weeks prior to examination. Limited evidence suggests that children under two years of age are more likely to develop cryptosporidial diarrhea[62,70,79] and that the disease is seasonal[62,80]. *Cryptosporidium* has also been responsible for epidemics of acute diarrhea in day-care centers in South Africa[81] and community outbreaks in Guinea-Bissau[79].

Limited published data are available from Sub-Saharan Africa on etiologic agents associated with persistent diarrhea. The relative contribution of specific pathogens to this ubiquitous problem is unclear and may vary regionally. A survey of hospitalized children with diarrhea in Somalia found that rotavirus, *Shigella* sp., and *G. lamblia* were significantly more common in acute than persistent diarrhea[66]; special stains for *Cryptosporidium* were not performed. A prospective, community-based one year survey in urban Guinea-Bissau found that *Cryptosporidium* was the only pathogen significantly more prevalent in children with persistent compared to acute diarrhea[62] and was associated with excess infant mortality which persisted into the second year of life[71]. This parasite was also found more commonly in children with persistent diarrhea in Bangladesh[76]. However, the available evidence suggests that *Cryptosporidium* is responsible for only a fraction of cases of persistent diarrhea[62,76]. Serial infections with different agents may underlie the development of some episodes of persistent diarrhea[4,76,82] as well as host factors including nutritional or immunological status. The role of enteroaggregative *E. coli* has not been adequately studied thus far.

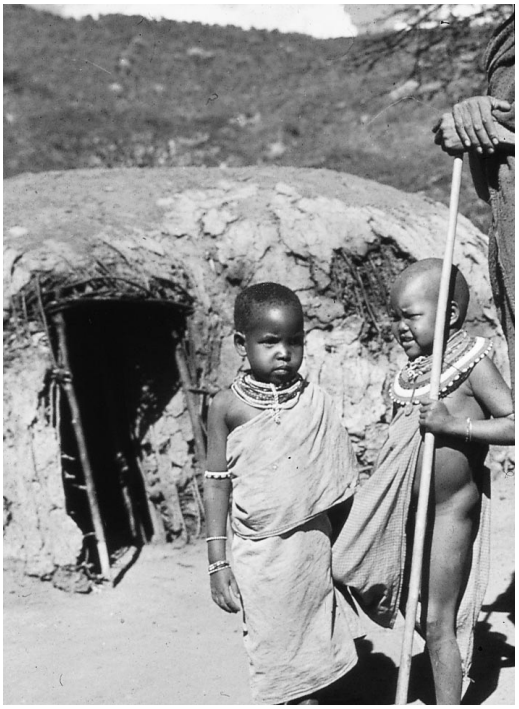


Table 4. Etiologies of childhood diarrhea in Sub-Saharan Africa

Pathogen	Frequency of isolation in subjects with diarrhea (%)	Ratio symptomatic: asymptomatic infection	Countries studied
None isolated	36 - 72		Central African Republic (C.A.R.), Djibouti, The Gambia, Guinea-Bissau, Somalia, Zambia, Dem. Rep. of the Congo
Rotavirus	2.8 - 27.8	2.6 - ∞	C.A.R., Djibouti, Ethiopia, Gabon, The Gambia, Guinea-Bissau, D.R.O.C.
Campylobacter sp.	0.2 - 24	0.7 - 4.6	C.A.R., Djibouti, The Gambia, Guinea-Bissau, Somalia, D.R.O.C.
Enterotoxigenic *E. coli*	<2 - 12.4	1.1 - 5.2	C.A.R., Djibouti, Ethiopia, The Gambia, Guinea-Bissau, Somalia, D.R.O.C.
Enteropathogenic *E. coli*	3.8 - 12.1	0.6 - 5.4	C.A.R., Djibouti, Guinea-Bissau, D.R.O.C., Zambia
Shigella sp.	1.5 - 9	1.0 - ∞	C.A.R., Djibouti, The Gambia, Guinea-Bissau, Somalia, D.R.O.C., Zambia
Salmonella sp.	1.2 - 4	0.01 - ∞	C.A.R., Djibouti, The Gambia, Guinea-Bissau, Somalia, D.R.O.C., Zambia
Aeromonas sp.	0.2 - 8	2.7 - ∞	Djibouti, The Gambia, Somalia, Zambia
V. cholerae O1	0 - 6	12 - ∞	The Gambia, Guinea-Bissau, Somalia, D.R.O.C.
P. shigelloides	2.0	4.0	Somalia
Y. enterocolitica	0 - 1.1	∞	The Gambia, D.R.O.C.
G. lamblia	4.0 - 2.6	0.7 - 1.6	C.A.R., Ethiopia, The Gambia, Guinea-Bissau, Somalia, D.R.O.C.
E. histolytica	2.2 - 20.3	0.7 - ∞	C.A.R., Ethiopia, Guinea-Bissau, Somalia, D.R.O.C.
Cryptosporidium	5.7 - 8.4	1.4 - 2.6	Guinea-Bissau, Liberia
S. stercoralis	2.1 - 4.5	1.6 - ∞	C.A.R., The Gambia, Guinea-Bissau
Isospora belli	0.6	0.75	Guinea-Bissau

Note: Data are derived from six prospective and two cross-sectional studies which included controls and provided a definition of diarrhea.

Risk factors

Breast-feeding, especially if this is the only source of nutrition, has been shown to protect children against the development of diarrhea in Africa[25,83,84], as elsewhere in the developing world[85]. In contrast, foods given for complementary feeding probably contribute to diarrhea in infants. The early introduction of milk-formula or solid food is often considered to increase exposure to enteropathogens[86] and has been associated with increased rates of acute diarrhea[5,25]. Studies in The Gambia in the 1970s demonstrated heavy contamination of gruels used as complementary foods in breast-fed infants[87,88]. Millet flour, cooking water, empty serving bowls, and even simmering gruel were all found to be contaminated with *E. coli*; colony counts of this and other organisms increased steadily with storage at room temperature[88]. Although these investigators speculated that contamination of complementary foods increased the risk of diarrhea, a subsequent study by the same group failed to document an association between water or weaning food contamination and higher rates of diarrheal morbidity[89]. Two more recent studies have found an increased risk of diarrhea associated with the consumption of maize-based weaning foods[83,90]. However, in one of these studies, this association was only significant in children living in rural communities[83]. The failure to demonstrate an association between the contamination of complementary foods and diarrhea in these studies may be due to a less comprehensive search for specific enteropathogens[86]. The use of fermented cereal-based weaning foods, which have been demonstrated to inhibit the growth of potentially pathogenic bacteria, especially enteropathogenic *E. coli*, represents a simple, locally acceptable measure that may prove to be useful in curtailing the proliferation of diarrheal disease pathogens in food [91,92]. Methods of food handling and storage, source, storage and use of safe water, and personal hygiene all contribute to the potential risk of developing acute diarrhea.

A case-control study of maternal behavioral risk factors for severe diarrhea in young children in Kinshasa, Democratic Republic of the Congo compared hospitalized patients less than three years old with acute diarrhea requiring rehydration to residential neighbor controls[93]. Although there was a trend toward lower maternal educational status among cases, all other socioeconomic and demographic characteristics were similar in the two study groups. Case households had inferior hygiene practices including improper disposal of children's feces, absence of toilet paper, and solid or liquid waste disposal within the living compound. Weaker associations with diarrhea included the presence of flies in the latrine area and visible stool around the latrine. Logistic regression demonstrated that the use of improper means of fecal and solid waste disposal and maternal ignorance of proper caretaker hygiene were significantly associated with diarrheal disease. Improper refuse disposal was also found to be associated with an increased prevalence of diarrhea in The Congo[83] and Nigeria[25,90]. An increased risk of diarrhea in households lacking soap was found in one study, but this was significant for disease only in children aged 5–14 years during the wet season[25]. Storage of food in proximity to household defecation sites was evaluated in one study in Nigeria and found to be significantly associated with acute diarrhea[90]. The relationship of hygiene practices to increased diarrhea risk has been shown elsewhere in Africa as well[18,26,94]. An uncontrolled study in the Sudan found a strong association between the presence of maternal complaints of gastrointestinal symptoms and the risk of diarrhea in her child[95]. Unfortunately this study did not include non-diarrheic controls and did not clarify whether the mother's symptoms preceded or followed the child's diarrhea episode.

The relationship between water source and quality with diarrhea has been addressed in a number of studies. Failure to purify drinking water by filtering, boiling, or the addition of alum was a risk factor for acute diarrhea in the dry season in only one[25] out of three studies reviewed.[83,93]. Bacteriological studies in rural Nigeria have shown consistent contamination of traditional water sources with fecal coliforms and *streptococci*, albeit varying with the patterns of rainfall[96]. Ponds, rivers, and unprotected springs tend to be more heavily contaminated than protected springs. The source of drinking water has been significantly associated with an increased risk of diarrhea in a number of studies[83,90,94]. In a comparison of urban and rural communities, this association held true only for the latter[83].

Recurrent episodes of acute diarrhea were significant risk factors for the development of persistent diarrhea in urban Democratic Republic of the Congo and rural Zimbabwe[5,29]. Similar results have been observed in Guatemala and India[32].

Limited data suggest that children in the 6 to 18 month age range are most likely to develop persistent diarrhea[5,29]; however, an association between age and increased rates of persistent diarrhea has not been consistently demonstrated in other developing countries[32]. No significant association with the age at which complementary foods were introduced and the risk of persistent diarrhea in studies done in Democratic Republic of the Congo and The Gambia[5,30]. The potentially protective role of breast-feeding has undergone limited study in Sub-Saharan Africa. Although no study has systematically evaluated the interaction between malnutrition and persistent diarrhea, at least one report found a longer duration of diarrhea in malnourished children[44]. Deficits in nutritional status appear to contribute to an increased incidence of persistent diarrhea in other regions of the developing world as well[32,97]. Failure to gain weight in the month before an acute episode of diarrhea was a significant predictor of progression of acute to persistent diarrhea in a study in Kinshasa, Democratic Republic of the Congo[5].

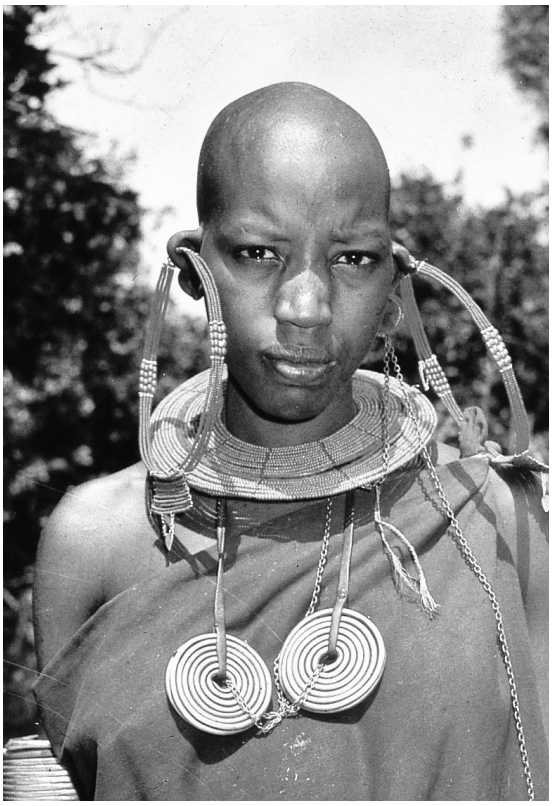
Few studies have evaluated the roles of socioeconomic and behavioral factors in the development of persistent diarrhea in Sub-Saharan Africa. No correlation between water source, behavioral factors, or socioeconomic status and persistent diarrhea was found in the above-mentioned birth cohort of infants in Kinshasa, Democratic Republic of the Congo[5]. This study did show a strong effect of underlying HIV infection on the risk of developing persistent diarrhea.

Cholera

In 1970, about a decade into the current (seventh) pandemic, *V. cholerae* El Tor struck West Africa (Guinea)[98] and then rapidly moved throughout much of the continent to involve 30 countries. Initially cholera spread along coastal regions in classic fashion, and later worked its way inland along trade and fishing routes. In 1971, approximately 150,000 people developed symptomatic infections with estimated case fatality rates of 10 to 15% or higher[99]. *V. cholerae* subsequently became endemic in Africa in regions where the appropriate conditions of temperature, humidity, rainfall, and population density existed.

V. cholerae is a marine organism which has the capacity to establish endemic foci in association with phytoplankton from which it may spread to humans. Since 1970, sporadic outbreaks of cholera have continued to plague Africa. In 1993, four south African countries Malawi, Zimbabwe, Mozambique, and Zambia accounted for nearly 85% of reported cholera cases on the continent[100]. Reports do not necessarily reflect the full extent of the disease burden in the affected areas as both poor surveillance and deliberate under reporting are known to occur. Even so, the number of cholera cases reported to the World Health Organization (WHO) increased 111% between 1993 and 1994 with a total of 28 countries reporting cases of cholera[101], and in 1994, Africa was the continent responsible for reporting the greatest proportion of cases worldwide. Large outbreaks have occurred in Somalia, Guinea, Guinea-Bissau, and the Rwandan refugee camps in Goma, Democratic Republic of the Congo. Although the total number of cases reported from Africa in 1995[102] was about 50% lower than in 1994[100], *V. cholerae* still remains a major contributor to epidemic diarrheal disease and mortality in Sub-Saharan Africa.

Cholera epidemics are often characterized by an initial high case-fatality rate because of inadequate case management for the rapidly and profoundly dehydrating illness it can cause[103-105]. In Mali in 1984, 36% of deaths occurred within the first 48 hours and an additional 36% during the subsequent five days of the outbreak[105]. Attack rates and mortality were highest in adults greater than 59 years old. Children between 1 and 14 years of age had attack rates similar to adults under 60 years but had a higher case-fatality, whereas no infants developed symptomatic cholera or died. The dramatic and highly publicized outbreak of cholera in the Rwandan refugee camps in Goma in 1994 followed a similar pattern with a high early case-fatality rate of 14.1% for all ages which decreased to 6.5% within one week (see below)[103]. In both examples, initial treatment was inadequate in the



majority of patients and exacerbated by the sudden appearance of large numbers of patients and poor preparedness of the health system[105,106]. As expected, the application of more vigorous rehydration measures and judicious use of appropriate antimicrobial agents were followed by declines in the case-fatality rates. Data on the number of deaths due to cholera notified to the WHO show a drop in the case-fatality rate in Africa from 15.7% in 1971 to 4.3% in 1995[102]. Although these figures are encouraging, the high initial case-fatality rates seen in the Goma outbreak underline the importance of early recognition and rapid responses to new cholera outbreaks.

Cholera has spread in Sub-Saharan Africa via well-known modes of transmission including contaminated water, food, and soiled hands (which in turn contaminate foods or fluids and amplify the inoculum) but also by activities such as body cleansing rituals during funerals and prolonged exposure to lake water[105,107 108-111]. Case-control studies have implicated the consumption of river or lake water[110], water purchased from vendors[110], well water[105], and left-over foods[105, 111] as risk factors for the development of cholera. Acidic sauces, hand washing with soap after defecation, and the consumption of treated water (with chlorine or boiling) reduce the risk of transmission[110,111]. In addition to the many community-based epidemics of cholera, nosocomial outbreaks with possible person-to-person spread secondary to overcrowded conditions and inadequate hygiene have been described[107,109]. In both reports, attempts were made to identify a common source of food or water but since *V. cholerae* could not be cultured from potential sources, the investigators concluded that person-to-person spread was the probable mechanism of transmission. One of these outbreaks involved a pediatric unit where, in contrast to an overall rate of 11.3% in the hospital, a case-fatality rate of 30% occurred in infants less than one year old[107]. These findings conflict with those of Tauxe et al. who found no deaths or cases in infants in a community-based outbreak in Mali[105]. Children, especially those younger than two years, were the group predominantly affected in three hospital outbreaks in Tanzania[109]. The Tanzanian nosocomial epidemics were implicated as the source of subsequent urban outbreaks.

The widespread use of antimicrobial agents in some regions was followed by the rapid emergence of resistant strains. Both of the nosocomial outbreaks as well as many of the community-based epidemics have been caused by strains of *V. cholerae* El Tor[106,107,112,113] that exhibit resistance to multiple antibiotics. During the cholera outbreak in Tanzania in October 1977, initial resistance rates to ampicillin, sulfa, and tetracyline were relatively low (15, 23, and 0%, respectively), but within four months, clinical treatment and prophylaxis failures were being observed with tetracycline[113]. Within two months, *V. cholerae* isolates exhibited high level in vitro resistance to ampicillin, sulfa, and tetracyline (86, 86, and 76%, respectively). The rapid rise in resistance was attributed to the widespread use of sulphonamides initially and then tetracycline for both the treatment and prevention of cholera. Similarly, after epidemic cholera reappeared in Kenya in 1980, mass tetracycline prophylaxis campaigns were carried out in affected regions. During subsequent outbreaks in 1982 and 1985 strains resistant to tetracycline, ampicillin, and sulfa drugs were frequently isolated[114,115]. These studies demonstrate the facility with which strains of cholera may develop resistance during outbreaks when there is heavy use of antibiotics for treatment or prophylaxis. They underscore the need for continuous resistance monitoring during epidemics and sound antibiotic utilization strategies.

Refugee camp associated diarrhea and dysentery

The outbreak in the Rwandan refugee camps provides many lessons about the rapid spread of deadly diarrheal disease under conditions of extreme crowding and the breakdown of social infrastructure. The camps were a setup for epidemic disease, and when cholera began in the second week of July 1994, its incidence rapidly rose, peaked within two weeks resulting in thousands of cases per day, and then declined in early August[103,106]. Approximately 85-90% of the more than 48,000 deaths which occurred in this four-week period were due to diarrheal disease.

Many problems contributed to the high early-case fatality rates including the use of narrow gauge intravenous (iv) needles for rehydration, inappropriate iv fluid, shortages of Ringer's lactate, slow rates of initial rehydration in cases with severe dehydration, inadequate emphasis on oral rehydration solutions (ORS) for rehydration of acutely dehydrated patients or for the continued hydration after initial rehydration, a lack of patient monitoring during hydration, nasogastric hydration with Ringer's lactate instead of ORS, and the use of antibiotics to which the cholera strain was resistant[106]. Medical personnel were thinly stretched and often inexperienced as indicated by the ordering of large quantities of antibiotics before sensitivity patterns had been determined. To make matters worse, the cholera outbreak was followed by an outbreak of dysentery caused by multiply resistant *S. dysenteriae* type 1 with significant secondary malnutrition and high mortality.

The problems encountered in this refugee camp draw attention to a number of special issues that are common to epidemics of diarrheal disease occurring in the setting of mass population migrations during civil disorders, natural disaster, and famine. Weaknesses of national health infrastructures lead to delays in treatment due to shortages of ORS, intravenous fluids, and appropriate antimicrobial agents. Responses to new outbreaks are often entirely left to non-governmental organizations or other outside agencies such as the World Health Organization. Problems with drug availability or the limited knowledge base of local health care providers leads to the inappropriate use of antibiotics. Inadequate systems exist for surveillance of resistant isolates. Deficiencies of basic public infrastructure and education contribute to the continued use of contaminated water or foods and failure to improve personal hygiene, sanitation, and safe water supplies. Finally, the dispersion and mobility of the affected populations coupled with inadequate roads, fuel supplies, and means of transportation for the provision of emergency fluids and supplies make it difficult to respond rapidly to epidemics with the necessary interventions[116].

Invasive diarrhea

Much of the recent literature on invasive (bloody) diarrhea and dysentery in Sub-Saharan Africa has focused on epidemic dysentery due to *Shigella dysenteriae* type 1. This organism appeared in northeast Dem. Rep. of the Congo in late 1979 and quickly spread within the country, reaching neighboring Rwanda and Burundi in 1981, and Tanzania in 1982[112,117-120]. Unlike endemic shigellosis, attack rates were higher in adults than children[117,119,120]. Case-fatality rates of 2–6% were reported but tended to be lower when appropriate therapy was used[119,120]. In Rwanda, case-fatality rates were highest in children and older adults[119], similar to epidemic *S. dysenteriae* in Latin America and the Indian subcontinent, whereas lower fatality rates were reported among children in Dem. Rep. of the Congo[120]. The epidemic continued to spread, and reached Zambia in July 1990[121]. Adults accounted for the majority of infected subjects although the proportion of infected children increased with time. At least 4% of the adults and 15% of children with dysentery admitted to the hospital succumbed to their illness. Review of surveillance data of seasonal epidemics from Burundi demonstrated an annual sharp increase in dysentery cases between September and December from 1980 to 1990[122] with *S. dysenteriae* type 1 the predominant pathogen isolated from subjects with acute bloody diarrhea in these outbreaks. The median age of cases was 22 years in 1990, and only 21% of the infected were less than five years old. Recent reports document the extension of the epidemic to southern Africa[123,124]. These outbreaks have been accompanied by a rise in hospital admissions of children with the hemolytic

uremic syndrome and a rise in dysentery-associated mortality rates, not noted in the previous reports, presumably due to inadequate case assessment.

Of 189 subjects with bloody diarrhea during an outbreak in Burundi in 1990, 69% had a pathogen identified; *S. dysenteriae* type 1 was the predominant isolate (43% of patients in whom a pathogen was identified)[122], but other *Shigella* spp. (26%) (predominantly *S. flexneri*) and, less commonly, *Campylobacter* spp. (4%) and *E. histolytica* (4%) were identified as well. Patients with *S. dysenteriae* type 1 were significantly more likely to have abdominal pain, more than 10 stools per day, and visible blood in their stool. Similarly, 48% of cases during a dysentery epidemic in Zambia were culture positive for *S. dysenteriae* type 1[121]. Following the cluster of cholera cases among Rwandan refugees in Goma, Dem. Rep. of the Congo in late July 1994, an outbreak of bloody diarrhea occurred, also largely due to *S. dysenteriae* type 1[116]. Dysentery was estimated to be responsible for almost 40% of the deaths during the first month of the influx of refugees into the camp.

Etiologic studies of endemic diarrheal disease in other parts of Sub-Saharan Africa which employed extensive microbiological methods found low rates of pathogens capable of causing invasive diarrhea such as other *Shigella* sp., *Salmonella* sp., and enteroinvasive *E. coli*[5,60,62,65,66,125]. In non-outbreak settings, *S. flexneri* was the most commonly isolated species of *Shigella* in many regions of Sub-Saharan Africa[65,67,126-128]; however, many studies did not identify the species of *Shigella* isolated[59-62,66,129].

Although selective media for the identification of *Salmonella* spp. and *Shigella* spp. have usually been used in studies of invasive diarrhea in Sub-Saharan Africa, special techniques to identify enterohemorrhagic or enteroinvasive *E. coli* have not been routinely used. Consequently, the roles these respective pathogens play in endemic and epidemic dysentery in this region remain ill-defined. *E. coli* 0157 was implicated as the cause of a waterborne outbreak of hemorrhagic colitis in South Africa and Swaziland in 1992[130]. This organism was isolated from 22.5% of stool specimens as well as cattle dung, water samples, and fly-infested cooked maize. In a prospective study in Kinshasa, Democratic Republic of the Congo[5], only one of 269 stool samples examined was positive for the Shiga-like toxin genes of enterohemorrhagic *E. coli* by DNA probe methods.

Shigellosis is typically spread by person to person contact or via contaminated food or fluids, and transmission of infection in Africa appears to be no different than elsewhere in the world. Multivariate logistic regression analysis of a case-control study of both adults and children during an epidemic in Zambia showed an independent association of two risk factors with dysentery: the presence of a family member previously ill with dysentery and obtaining drinking water by dipping with a cup[121]. Recent contact with a person suffering from dysentery was also found to be a risk factor for symptomatic infection with *S. dysenteriae* type 1 in Burundi [122]. In addition, infection was also significantly associated with a history of one or more episodes of diarrhea in the last 12 months.

Since *Shigella* is highly host adapted to humans, it is reasonable to assume that spread throughout the continent occurred via human travel and transport of organisms. Why it took 10 years to move from Central to southern Africa is uncertain. Sporadic cases in rural areas might well be missed; epidemics accompanied by high mortality and by renal failure, as in the case of *S. dysenteriae* type 1, would be less likely to be missed.

Multidrug resistant shigellosis

Transferable multidrug resistance was first described among *Shigella* in Japan in the mid 1950s [131], and has remained a major problem ever since. Multiresistant strains of *S. dysenteriae* type 1 were isolated with high frequency from subjects with bloody diarrhea during the initial Central African epidemics in the late 1970s and early 1980s[117,118,120]. Extensive surveillance of *Shigella* and *Salmonella* isolates from Kigali, Rwanda between 1976 and 1982 demonstrated a progressive rise in multiresistant strains[132]. Examination of six strains of *S. dysenteriae* type 1 from Congolese patients early in the Central African outbreak identified a single autotransferring plasmid which conferred resistance to ampicillin, chloramphenicol, and tetracycline[118]. These strains were also resistant to streptomycin and sulfonamides but this resistance was non-transferable. Interestingly, this plasmid appeared identical to a resistance plasmid identified in isolates from an epidemic of shigellosis in Somalia in the early '60s. Shortly after the introduction of trimethoprim-sulfamethoxazole (TMP-SMX) as the treatment of choice, an increase in plasmid-mediated resistance to trimethoprim was observed[133]. This led to the widespread use of nalidixic acid and the predictable emergence of resistance to this drug as well[134]. More recently isolates of *S. dysenteriae* type 1 from Burundi were found to be highly resistant, whereas other *Shigella* spp. were not and often were still sensitive to ampicillin[122]. Similarly, in Zambia, 48% of the 88 stool specimens from dysenteric patients yielded *S. dysenteriae* type 1 resistant to ampicillin, chloramphenicol, streptomycin, sulfisoxazole, tetracycline, and TMP-SMX[121]. Norfloxacin was at least as effective a therapy for multidrug resistant shigellosis as nalidixic acid in an open trial in Rwanda[135] but resistance to this and other newer fluoroquinolones may rapidly emerge if their use becomes widespread. In addition, fluoroquinolones and other new drug options are of limited availability and expensive[136]. A common feature of these outbreaks has been the apparent rapid adaptation of the pathogen to changes in the utilization of antimicrobials. However, no study has estimated the contribution of inappropriate antibiotic use to the development of resistance.

Drug use and misuse

In many communities, modern pharmaceutical agents are a commonly used first line of therapy for the home treatment of diarrhea or they serve as an alternative when traditional remedies fail. Potential sources of medications include pharmacists, health centers, or hospitals, relatives or friends with unused supplies, locally trained nurses, licensed dispensers, shopkeepers, market sales people, and unlicensed drug salesmen who buy drugs in major cities and then sell them in rural villages [137,138]. Extensive evidence exists to suggest that the use of antimicrobials and antimotility drugs for the treatment of diarrhea is widespread and often significantly exceeds that of ORT[139-143]. Factors influencing the use of unprescribed medications include drug availability, cost, and cultural beliefs. A survey of pharmacy utilization in Ethiopia found that the type and price paid for drugs were associated with level of education of the purchaser and economic constraints[144].

A study of the Mende of Sierra Leone revealed that the function of Western medicines has been reinterpreted based on traditional beliefs of disease causation and treatment[138]. Factors influencing the use of Western drugs by the Mende include their reputation for curing friends or relatives, the size of pills, and the color of the medication. Combinations of cultural perceptions about disease causality and treatment, drug availability, anecdotal knowledge of curative efficacy, and cost constraints all enter into the decision to buy Western medications for treatment of diarrhea and other diseases. In addition, families may be more likely to resort to antimicrobial agents when their child's diarrheal episode is prolonged[137]. The use of Western medicines by inadequately trained personnel or caretakers is often characterized by incorrect dosages (both low and high) and, frequently, a brief duration of therapy that is insufficient for the eradication of the diarrheal pathogen. The potential consequences of such extensive drug use include treatment failure caused by inappropriate drug selection, combinations or dosing errors, serious adverse effects or death from overdosage or the use of counterfeit drugs, and, assuming the drugs are bioactive, an increase in antibiotic resistance in pathogenic and non-pathogenic bacteria[138].

Antimicrobial resistance

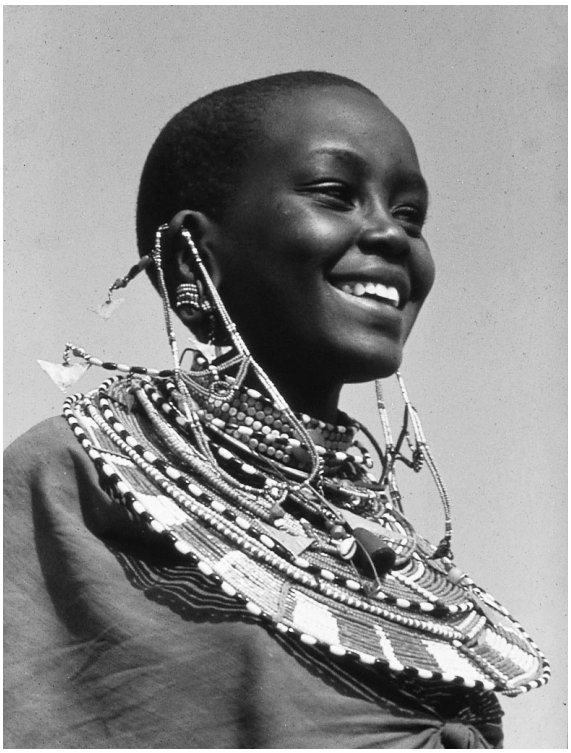
Few investigations of antimicrobial resistance of enteric pathogens have been reported from Sub-Saharan Africa with the notable exceptions of studies of epidemic cholera and invasive diarrhea discussed elsewhere. High rates of resistance to commonly used, inexpensive, oral antimicrobial agents such as ampicillin, tetracyclines, and trimethoprim-sulfamethaxosole were observed in isolates of enteroadherent *E. coli*, ETEC, EPEC, and *Shigella* spp. in a survey in Somalia[165]. Similarly, high overall rates of resistance, often to multiple drugs, were seen in isolates from children with acute diarrhea in Nigeria[129]. Unfortunately, detailed resistance patterns of each pathogen were not reported. High levels of resistance to commonly used antibiotics have also been observed in *Shigella* spp. in Nigeria[128] and Ethiopia[145]. Although reported resistance to nalidixic acid is low[126,128], this may increase rapidly with more widespread use of this drug for treatment of shigellosis[134]. Rates of resistance tend to be less for *Salmonella* spp., at least in the Horn of Africa[65,145]. There appears to be considerable regional variation in the sensitivity patterns of C. *jejuni* to erythromycin, with resistance rates of 79.2 and 0% in Nigeria[146] and Djibouti[65], respectively. Earlier data from Nigeria showed a much lower rate of erythromycin resistance of 18%[147]. The increased prevalence of strains exhibiting multiresistance to commonly available, less costly oral antibiotics represents a growing obstacle to the simple, cost-effective therapy of invasive childhood diarrheas in Sub-Saharan Africa. The alarming increase in rates of resistance of many diarrheal pathogens may relate to the frequent use and abuse of antibiotics.

Treatment and Prevention

Home case management and traditional healers

The mother or another caregiver usually provides initial management in the home. Major decisions are generally made by the mother although she may consult the child's father, her mother-in-law, other relatives, or neighbors[148,149]. Initial therapeutic measures are consistent with and derive from the folk perception of the cause and severity of the disease. The educational level of the mother may also influence decisions. For example, in a study of home management of diarrhea in Nigeria, Yoruba mothers with a higher level of education were more likely to use a combination of Western and traditional treatments, although very few mothers were inclined to use Western medicine alone[150]. Illiterate mothers in rural Sudan were more likely than literate mothers to stop breastfeeding or use incision and cautery of the gums where teeth are erupting as treatments for diarrhea[151]. Antimicrobial agents are frequently the first-line treatment of diarrhea in the home, followed by herbal remedies and, last of all, ORS[20,137,152]. One study showed that antibiotics were administered on 54.5% of days with diarrhea, local herbs on 27.7%, and ORS was only given on 14.8%[20]. Very young children and those with multiple episodes of diarrhea were more likely to receive combinations of treatment, especially antimicrobial drugs and ORS. Although the frequency of usage varies, antibiotics and herbal teas clearly play a central role in the home management of diarrhea in several Sub-Saharan countries, even though traditional treatment practices have been associated with a higher risk of death from diarrhea[152].

Despite the efforts of international health agencies to promote the home use of ORS, this intervention still remains an underutilized treatment in many areas of the developing world. Surveys of caregivers in Sub-Saharan Africa have found wide differences in the awareness and utilization of ORS for treatment of childhood diarrhea[153-155]. A comparative survey of multiple countries in the developing world found that the frequency of home use of ORS in six countries was in the range of 21 to 33%[155]. A notable exception was Lesotho, where two-thirds or more of children with diarrhea were given ORS and herbal medicine was used much less frequently than in all the other sites. This may have been a result of earlier interventions by the Ministry of Health which, although aimed at promoting the use of ORT in government facilities, may have resulted in increased awareness of ORS in the community[156]. The survey also found that ORS was often reserved for the treatment of children who were judged by their caretakers to be very sick[155] . None of these investigations included systematic observations of treatment practices in the home, an approach that may yield more accurate information on caretaker practices. ORS use often varies from town to town within a



single indigenous population[157], and is less common in populations without previous health education[20]. On the positive side, the home management of childhood diarrhea with ORT or sugar-salt solution SSS can be increased with public health education[158,159].

However, there are dangers in the home use of ORT, including inappropriate preparation (electrolyte concentration) or errors of administration (usually insufficient volume). Rates of correct preparation of ORS and SSS in the home vary widely. A study in Nigeria found that only 12.7% of people interviewed were able to correctly describe how SSS is prepared although almost all of them were aware of ORT[160]. In Zimbabwe, although nearly half the respondents were able to provide a recipe for SSS, only 12% gave the correct formulation[154]. An analysis of 147 samples of SSS revealed that only 26% had both sodium and glucose concentrations in the safe and effective ranges[154]. Although only 12% of respondents were initially able to make a correct SSS, 73% were able to recall the correct recipe they had been taught when revisited, but this decreased with time. On the other hand, in Conakry, Guinea, two-thirds of the study population correctly prepared ORS or SSS in the home[161].

In addition to improper preparation and the associated threat of electrolyte disturbances, the quantity of ORS used in the home may also be inadequate[159,161,162]. Despite high rates of correct preparation, Dabis et al. found that only 40% of children were treated with sufficient amounts to correct or prevent dehydration[161]. A study in Lesotho of home management of dehydration initiated ORT in the clinic setting and provided education to the mothers regarding the preparation and administration of ORS[159]. Mothers were supervised mixing a batch of ORS in the clinic and then were sent home with a liter of ORS in a clean bottle. The majority of the children (69%) received a minimally acceptable amount to maintain hydration. Most children were fed and given other liquids in the first 24 hours, and the majority either improved or did not worsen. Acceptance of the taste of ORS, as reported by the mothers was low with about 60% reporting that their children did not like the taste. The lack of acceptance of the taste may reflect the mother's perception and not that of the patient, but will likely have a negative influence on ORS usage. Recall of the amounts to give in different diarrhea scenarios was poor. Since the amount administered by the mothers was observed to be nearly the same for children of all ages, younger children tended to receive greater amounts based on their weights.

Treatment in the hospital or clinic

Health centers, hospitals, and private physicians are additional important sources of advice and prescriptions for the therapy of childhood diarrhea outside the home[141,161,163-165]. However, due to limited access, long waits for attention, misgivings about the effectiveness of Western medicine, and cultural dependency on traditional methods, the formal health sector is often used as the last resort in many communities[140]. A greater distance from health services was associated with an increased likelihood that no action involving the purchase of an antidiarrheal treatment would be taken for a child's diarrhea in rural Zimbabwe[164]. Unfortunately, inappropriate therapeutic recommendations are common and when the gravity of the child's illness is so severe that any treatment may fail, families may quickly lose confidence in medical centers. Nevertheless, hospitals and health centers remain a major alternative especially when home or traditional treatments fail. Episodes of greater severity may be more likely to result in the use of formal sector health facilities[161,163].

Health workers frequently fail to provide ORT or to advise caretakers to administer it at home [161,162]. When ORS use is advised, there is often a greater emphasis on how to prepare ORS at home than on how much should be given, how long ORT should be continued, how to recognize severe dehydration, or the importance of continuing feeding during the diarrhea episode[162]. The lack of continuing education in appropriate interventions, language barriers when health clinics are staffed by personnel who are not familiar with the local language, and financial constraints all limit the quality of care provided.

Various approaches have been tried to improve the delivery of diarrheal disease care in hospitals and clinics. Education of clinical staff can reduce the in-hospital use of intravenous fluids for dehydration, increase the use of ORS for mild-moderate dehydration, and decrease costs at least temporarily[166]. Developing an oral rehydration therapy unit for first line therapy of children with diarrhea in Lesotho resulted in a significant decline in hospitalization rates[166]. Cereal-based ORS has been tried on an even more limited basis in Sub-Saharan Africa[167-169]. The overall assessment of programmatic attempts to control diarrheal disease in Sub-Saharan Africa is a partial success. Each of these modalities–staff education, the use of specialized ORT units, and cereal-based ORS–represents opportunities to improve the delivery of diarrheal disease care.

Diarrheal disease control programs

Nearly all the countries in Sub-Saharan Africa now have diarrheal disease control programs, at least on paper[11]. These have largely employed a WHO-endorsed case-management strategy which emphasizes ORT, probably the easiest intervention to implement. Additional measures including improved nutrition with a focus on breast-feeding and safe weaning foods, better personal and domestic hygiene, and the provision of safe water supplies are being gradually introduced. These are all more difficult to effect. Measuring the impact of water supply, improvements in sanitation, and public health education on diarrheal disease is methodologically complex[170,171]. Study design (cross-sectional versus longitudinal), lack of adequate controls, confounding variables, type of health indicator chosen for study, health indicator definition, health indicator recall, failure to stratify by age, and failure to record water or sanitary facility usage are some of the factors that complicate interpretation and generalization of the effects of community intervention programs.

A primary health care project in rural Tanzania trained village health workers to provide health education to mothers during home visits every six to eight weeks targeted to the recognition of symptoms of acute respiratory infection and the initiation of early treatment or referral of severely ill children [172]. Although diarrheal disease was not a focus of the intervention, there was a 50% reduction in diarrhea-specific mortality in the intervention areas one year later. A community-based primary health care program in The Gambia which made use of trained village health workers to recognize and treat common maladies, encourage immunization, and provide nutritional education found small reductions in infant and child mortality in both intervention and control communities[173]. Because of the lack of a difference between the two study areas, the reduction in mortality could not be attributed to the intervention.

In rural Dem. Rep. of the Congo, an intervention consisting of public health messages intended to influence personal and domestic hygiene practices led to an 11% reduction in the relative risk of a child being reported with diarrhea during the post-intervention surveillance period[21]. The intervention group experienced fewer days ill with diarrhea and a trend toward shorter duration of illness. The greatest differences were observed in children 24 to 35 months old, as in Bangladesh[174]. These studies suggest that personal or domestic hygiene factors including the availability and use of safe water supplies may be more important for older than younger children.

The Imo State Drinking Water Supply and Sanitation Project in Nigeria, a collaborative effort involving several state governments with UNICEF assistance, evaluated the effects of improved water source (boreholes with hand pumps), ventilated improved pit latrines, and supportive hygiene and health education on the prevalence of diarrhea and malnutrition[175]. These interventions did not appear to have an impact on diarrheal prevalence but did lead to a progressive decline in the proportion of children aged less than three years with weight-for-height below the 80% reference value. The use of boreholes as the only source of drinking water decreased significantly as the distance from the home to the borehole increased[158]. A major problem with this study was the reliance on biannual surveys for the collection of all morbidity data.

A case-control approach was used to study the effect of improved water and sanitation facilities on diarrheal morbidity in Malawi[176]. The risk of attending a clinic because of acute diarrhea was reduced by 20% in children with access to improved sanitation and water supplies. This effect was not statistically significant, perhaps because of the small study sample size. However, a similar estimate of the reduction in diarrheal morbidity (22%) was obtained from a review of worldwide studies of the impact of sanitation[177]. These findings are moderately encouraging; however, assessing the effect of sanitary, water, and public health education interventions on morbidity and mortality from diarrheal diseases remains a challenge for investigation. Combined approaches are suggested but are likely to be costly and difficult to analyze. The efficacy of public health campaigns to increase awareness and ORT use is more easily examined.

An evaluation of the effect of the diarrheal control program in Nigeria found a 9% decline in the incidence of diarrhea between 1986 and 1989, but this decrease was not statistically significant[141]. The diarrheal control program failed to lead to a high rate of ORT use in the home or health facilities. Caregivers from both the intervention and control areas in the Imo State Drinking Water Supply and Sanitation Project were found to have a greater awareness and use of ORS, improved knowledge of fecal transmission of disease, and better hygienic practices during the course of the study[158]. These studies suggest that the awareness and home use of ORS can be influenced through public health education programs, albeit with difficulty.

In the Democratic Republic of the Congo, the Centers for Disease Control's program for Combating Childhood Communicable Diseases (CCCD) was successful at increasing the awareness of ORS, its use in the home, and the use of selected health services[178]. Although this project appeared to improve awareness and utilization of ORS, it was not possible to assess its impact on mortality due to diarrhea because of inadequacies with the collection of pre-intervention mortality data and the combining of the control and intervention groups into a single program area[179]. In contrast to the possible successes in Democratic Republic of the Congo, the CCCD program in Liberia did not result in an increased use of SSS or more fluids during acute episodes of childhood diarrhea despite an apparent increase in awareness of ORT[180]. Mass communication techniques which incorporate local perceptions of diarrheal disease management, together with increased availability of ORS salts and educational efforts to teach proper ORS preparation and use, can stimulate increased use of ORT in rural areas of Sub-Saharan Africa[181]. Assessing the effect of these interventions on diarrheal disease morbidity and mortality requires carefully designed prospective studies which combine qualitative survey with observational data. Most important, the duration of the intervention, and the intensity with which it is promoted, must be sufficiently long and consistent to expect to see a measurable impact.

Conclusions and Research Agenda

Diarrheal disease is a major cause of childhood morbidity and mortality in Sub-Saharan Africa. Although the limited evidence available suggests that mortality rates have dropped in the last decade, the impact of civil war, social disruption, famine, and epidemics (cholera, antibiotic-resistant dysentery) can be locally and temporally profound. Although not a focus of this review, the burgeoning HIV epidemic will no doubt result in large increases in the rates of morbidity and mortality from acute and persistent diarrhea throughout Sub-Saharan Africa during the next decade. This impact is likely to be detected in both HIV-infected and uninfected infants and children. Potential areas for future research and interventions are listed below. These have been organized into general categories that may be overlapping. Suggestions are also provided for methodologic changes that are needed to strengthen the quality of research performed.

Cholera:

• Surveillance systems for detecting new epidemics and continuously monitoring for changes in antibiotic sensitivity patterns;

• Use of rapid diagnostic tests for the detection of cholera;

• Studies of local practices and perceptions of diarrhea in order to devise strategies to interrupt transmission, and

• Emergency plans for rapid response to new outbreaks on a regional level including protocols designed to decrease mortality in refugee camp outbreaks.

Invasive diarrhea:

• Studies to identify reservoirs of invasive enteropathogens and their routes of transmission which will serve as a basis for the design of focused interventions for the prevention of invasive diarrhea;

• Studies of the role of specific pathogens, such as enterohemorrhagic or enteroinvasive strains of *E. coli*, to determine what role they play in the epidemiology of invasive diarrhea;

• Prospective studies of risk factors for symptomatic invasive diarrhea;

• Studies of the rates of asymptomatic infection and its impact on transmission within households;

• Use of rapid diagnostic tests which distinguish invasive from watery diarrhea, and

• Interventions directed at interrupting the spread of dysentery within communities, refugee camps, and hospitals.

Persistent diarrhea:

• Use of carefully constructed definitions of an episode of diarrhea to evaluate the impact of persistent diarrhea on child survival;

• Studies which examine the interactions between acute, recurrent, and persistent diarrhea as well as the impact of appropriate case management of acute and recurrent acute diarrhea;

- Improved methods for the assessment of specific host risk factors such as:
    - malnutrition
    - diet
    - acute and recurrent episodes of diarrhea
    - HIV status of child and caretaker
    - parental health
    - socioeconomic status
    - personal hygiene practices
    - safe water availability and use
    - complementary feeding practices
    - breast-feeding
    - specific micronutrient deficiencies
    - malaria

- Research to better understand how these factors interact to cause or exacerbate diarrhea and its complications as a prelude to identify potential focuses for interventions;

- Further evaluation of nutritional management algorithms for treatment of persistent diarrhea in the community setting;

- Evaluation of the effect of single or combined micronutrient supplement interventions on the course of persistent diarrhea, and

- Interventions combining multiple modalities to decrease mortality and morbidity from persistent diarrhea.

Modifying patterns of treatment:

- Interventions to improve the recognition of signs of severe dehydration in the home to prompt referral to health services;

- Identification of barriers to medical care access;

- Inclusion of traditional healers and other untrained practitioners in the provision of appropriate health care;

- Defining local perceptions of the causation, severity, and treatment of diarrhea and their incorporation to planned interventions for disease control;

- Interventions to promote the quality use of antibiotics and to eliminate the use of antimotility agents for the treatment of diarrheal disease;

- Evaluations of the impact of public health campaigns on the proper preparation and use of ORS (these campaigns must incorporate local cultural perceptions of diarrhea causation and address the frequent lack of appropriate measuring utensils in the home and the cost of ORS;

- Studies of the efficacy and safety of low osmolarity ORS for the treatment of acute diarrhea and cholera;

- Randomized, controlled studies of the safety and efficacy of traditional remedies for childhood diarrhea, and

• Interventions to improve the delivery of diarrheal disease care in hospitals and clinics by means of staff education, the use of specialized ORT units, and cereal-based ORS.

Interaction between malnutrition and diarrhea:

• Interventional studies to improve breast feeding practices;

• Efforts to identify locally acceptable, safe, and inexpensive weaning foods;

• Interventions to improve access to varied and nutrient balanced diets;

• Use of appropriate dietary management principles in the treatment of diarrheal disease episodes with an emphasis on the need to continue feeding during episodes of diarrhea, and

• Greater emphasis on multinutrient interventions which include monitoring for potentially detrimental nutrient interactions.

Prevention of diarrhea:

• Interventions to increase the availability and use of safe water supplies*;

•Efforts to improve personal and domestic hygiene including campaigns to promote the appropriate use of soap*;

• Efforts to improve weaning practices*;

• Evaluations of improved food and water handling and storage methods and practices*, and

• Immunization programs for cholera and other enteric pathogens when new, effective vaccines become available.

General:

• Interactive multidisciplinary research approaches involving social science, economics, public health, and biomedical science perspectives;

• Exploration of the use of government action to limit the availability of antidiarrheal drugs;

• Programs to train health care personnel in the appropriate management of childhood diarrhea, and

• Development of competence in conducting cost-effectiveness evaluations.

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* The effects of these interventions on morbidity and mortality attributable to diarrheal disease need to be evaluated with well-designed, prospective, controlled studies which combine surveys with observational data and need to be sufficiently long in duration and consistent in order to be able to detect a difference.

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