Frederick J. Angulo, Section Editor

# Invasive Non-Typhi *Salmonella* Disease in Africa

**Susan C. Morpeth,[1,4,6] Habib O. Ramadhani,[4,5] and John A. Crump[1,2,3,4,5]**

[1]Division of Infectious Diseases and International Health, Department of Medicine, Duke University Medical Center, and [2]Duke Global Health Institute, Duke University, Durham, North Carolina; [3]Enteric Diseases Epidemiology Branch, National Center for Zoonotic, Vectorborne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [4]Kilimanjaro Christian Medical Centre and [5]Kilimanjaro Christian Medical College, Tumaini University, Moshi, Tanzania; and [6]Pathology Queensland Central Laboratory, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia



**Invasive non-Typhi *Salmonella* is endemic to sub-Saharan Africa, where it is a leading cause of bloodstream infection. Some host risk factors have been established, but little is known about environmental reservoirs and predominant modes of transmission, so prevention strategies are underdeveloped. Although foodborne transmission from animals to humans predominates in high-income countries, it has been postulated that transmission between humans, both within and outside health care facilities, may be important in sub-Saharan Africa. Antimicrobial resistance to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol is common among non-Typhi *Salmonella* strains; therefore, wider use of alternative agents may be warranted for empirical therapy. Development of vaccines targeting the leading invasive non-Typhi *Salmonella* serotypes Typhimurium and Enteritidis is warranted. The clinical presentation of non-Typhi *Salmonella* bacteremia is nonspecific and, in the absence of blood culture, may be confused with other febrile illnesses, such as malaria. Much work remains to be done to understand and control invasive non-Typhi *Salmonella* disease in sub-Saharan Africa.**

*Salmonella enterica* subspecies *enterica* includes >2400 serotypes found in humans and other warm-blooded animals. Non-Typhi *S. enterica* serotypes are abbreviated using their serotype name—for example, *Salmonella* Typhimurium [1].

Non-Typhi *Salmonella* (NTS) is among the 3 most common pathogens causing bacterial bloodstream infections in adults and children in sub-Saharan Africa [2, 3]. Children <3 years old and human immunodeficiency virus (HIV)–infected adults carry most of the burden of invasive disease, and mortality among these groups is high. This contrasts with developed countries, where NTS disease is usually a self-limited diarrhea, and mortality is lower.

## BURDEN OF DISEASE

Invasive NTS disease is endemic to rural and urban sub-Saharan Africa. The burden of mortality due to childhood invasive bacterial disease may be greater than that due to childhood malaria in some African communities [4]. In rural Kenya, the estimated minimum incidence of bacteremia was 505 cases per 100,000 person-years in the age group of <5 years old, of which 88 cases per 100,000 person-years were NTS bacteremia. In rural Mozambique, the incidence of childhood bacteremia was 425 cases per 100,000 person-years among children aged <15 years, and within this category, NTS incidence accounted for 120 cases per 100,000 person-years [3]. The true incidence of bacteremia is likely to be 2–3 times this figure, because the incidence of bacteremia among children who die before reaching the district hospital was unable to be ascertained in either study [3, 4]. In an evaluation of the impact of pneumococcal conjugate vaccine in the Gambia, an incidence of NTS bacteremia of 262 cases per 100,000 person-years among children aged ⩽29 months was demonstrated [5]. In Uganda, NTS bacteremia was reported to be rare among adults with $CD4^+$ T-lymphocyte counts (CD4 cell counts) >500 cells/$mm^3$, but the incidence was 500 cases per 100,000 person-years among adults with CD4 cell counts of 200–500 cells/$mm^3$ and was 7500 cases per 100,000 person-years among adults with CD4 cell counts <200 cells/$mm^3$ [6].

Case-fatality estimates for invasive NTS disease among hospitalized patients in Africa have been in the range 4.4%–27% for children [5, 7–9] and 22%–47% for adults [10, 11]. Meningitis case-fatality rates may be higher for NTS than for any

Received 17 February 2009; accepted 13 April 2009; electronically published 10 July 2009.

Reprints or correspondence: Dr. John A. Crump, Div. of Infectious Diseases and International Health, Dept. of Medicine, Duke University Medical Center, Box 102359, Durham, NC 27710 (crump017@mc.duke.edu).

**Clinical Infectious Diseases 2009; 49:606–11**

1058-4838/2009/4904-0018$15.00
DOI: 10.1086/603553

other common cause of bacterial meningitis. For example, in Malawi, 64% of neonates with NTS meningitis died, compared with 26% of neonates with group B *Streptococcus* meningitis [12].

Although these studies provide some insight into the burden of invasive NTS disease in Africa, most studies have focused on high-risk groups, such as young children and HIV-infected adults. The actual incidence is likely to vary by population prevalence of HIV infection, local conditions, and age distribution. The incidence of invasive NTS disease in sub-Saharan Africa is likely to be higher than the incidence of typhoid fever, which has been estimated to be 50 cases per 100,000 person-years in Africa [13]. Furthermore, hospital-based studies suggest that typhoid fever may be considerably less common than is invasive NTS in sub-Saharan Africa [14].

Data on the frequency of complications of NTS bacteremia in Africa are limited. Meningitis, septic arthritis, and osteomyelitis have been described [7, 15–17], especially among children, for whom NTS may be a more common cause of septic arthritis than *Staphylococcus aureus* [18]. Gordon et al [11] investigated 100 Malawian adults with NTS bacteremia for focal suppurative disease and did not identify any localized NTS infections at initial presentation.

Of 2517 children with NTS bacteremia in Malawi during 1998–2004, 85% were aged <36 months and an estimated 19%–35% were HIV infected [10]. During the same period, 2439 adults with NTS bacteremia were identified, and an estimated 95%–98% were HIV infected. A South African autopsy study of 50 patients who died and had a premortem clinical diagnosis of tuberculosis revealed that 94% were HIV infected and 23% of HIV-infected patients were harboring splenic NTS [19].

## RISK FACTORS AND PREVENTION STRATEGIES

Risk factors for NTS infection in Africa (Table 1) have not been well characterized; consequently, evidence-based prevention interventions are limited. Small African studies and evidence-based prevention studies of NTS in more-developed countries may provide clues until more data from Africa are available.

Prospective studies of enteric NTS infection that investigate risk factors for development of bacteremia are limited. A North American study noted a bacteremia incidence of 6% among infants with NTS diarrhea, but modifiable risk factors were not identified [21].

### Environmental Risk Factors

***Food and water.*** Seasonal peaks of NTS disease occur with the rainy season among both adults and children [7, 10, 12, 22], suggesting that environmental risk factors are important. Fecal organisms are found at the highest concentrations in drinking water sources in Africa at the onset of the wet season [23], and this may correspond to increased risk of waterborne NTS. Protection of source water; increased access to centrally treated safe water; strategies such as the use of narrow-mouthed, spigoted containers for water storage [24]; and treatment of water at home by chlorination, solar disinfection, filtration, flocculation, or a combination of measures may reduce the risk of diarrhea [25].

Numerous outbreaks of foodborne illness due to NTS have been studied in industrialized countries and also have been described in Africa. Meat, eggs, produce, and dairy products have all been implicated as vehicles for transmission. NTS infect or colonize most mammalian species. Food animals, such as chickens, have been a focus of efforts to reduce transmission of NTS to humans in developed countries [26]. NTS has also been isolated from cattle, goats, sheep, and pigs in African slaughterhouses. Identification and management of hazards, facilitated by microbiological sampling at critical control points from farm to fork, have been used in both developing and industrialized countries to improve food safety and to control NTS disease [27].

***Zoonotic transmission and transmission between humans.*** Animal contact, particularly handling of young chickens by children, is a well-established risk factor for acquisition of NTS disease in industrialized countries [28]. Although not often considered a common risk factor for NTS infection in studies of developed countries, apparent transmission between humans has been suggested to be relatively more important in Africa [22, 29]. Kariuki et al [22] demonstrated carriage of identical

**Table 1. Risk Factors for Non-Typhi *Salmonella* Bacteremia in Africa**

| Risk factor category, risk factor | Grade of evidence[a] | |
|---|---|---|
| | Children aged <3 years | Older children and adults |
| Environment | | |
| Food and water | B | B |
| Hospital-acquired infection | B | B |
| Direct and indirect animal contact | C | C |
| Transmission between humans | C | D |
| Host | | |
| Age[b] | A | D |
| HIV infection | A | A |
| Malnutrition | A | … |
| Sickle cell disease | … | C |
| Malarial anemia | B | … |
| Schistosomiasis | … | D |
| Recent antimicrobial use | B | C |

**NOTE.** An ellipsis (…) indicates lack of data. HIV, human immunodeficiency virus.

[a] Levels of evidence were estimated from African studies included in this review and were classified according to the grades of the Oxford Centre for Evidence-based Medicine [20].

[b] For older children and adults, the risk factor is old age.

strains of NTS in the stool of human household contacts of children with invasive disease and a lack of such strains in environmental and domestic animal sampling from the households, although a common source from food or water could not be ruled out. Asymptomatic carriers of NTS have been described in Africa [30]. A Kenyan study of NTS carriage at admission to the hospital found that 20 (3.6%) of 556 children but none of 111 adults carried NTS [31]. In developed countries, it is known that children are likely to excrete NTS in their stool for several weeks after recovering from enteric infection.

***Hospital-acquired infection.*** Outbreaks of NTS disease have been reported in hospitals in many parts of the world, occurring among patients who are admitted with a different diagnosis. Outbreaks of hospital-acquired NTS can be particularly severe on pediatric wards in developing countries, where children may be malnourished and have other host risk factors. In African hospitals, food is often provided by a patient's family. Although few studies have examined risk factors for infection in hospital outbreaks, contaminated food and person-to-person transmission have been considered. High death rates are frequently observed, especially when outbreaks are caused by strains of NTS resistant to the local empirical therapy [17]. Of 360 adult and pediatric patients with hospital-acquired diarrhea in a Kenyan hospital in 1988, 10% of cases were due to *Salmonella* species and 2.5% to *Shigella* species. Among children aged 6 months to 6 years, recent antimicrobial use and crowded living conditions at home were associated with hospital-acquired diarrhea due to *Salmonella* or *Shigella* species. Among adults, sharing a hospital room with somebody who has diarrhea and a history of previous hospitalization were associated with hospital-acquired *Salmonella* or *Shigella* diarrhea [31]. Prevention strategies could include patient and visitor education regarding personal hygiene and food preparation and storage, provision of safe drinking water, hand washing before and after patient contact by health care workers, thorough cleaning of the hospital environment, reduction in crowding, avoidance of sharing beds, increasing the number of health care workers, adequate disinfection of reusable equipment, surveillance of NTS infection, and isolation of identified cases [17, 32].

### Host Risk Factors

***Age.*** Children and infants <3 years old are particularly at risk for invasive NTS disease [3–5, 7–10]. Endovascular infections with NTS have been described in adults aged >50 years in industrialized countries. Older age may also be a risk factor in African populations but is dominated by HIV-associated NTS disease among younger adults.

***Exposure to antimicrobial agents.*** Recent use of antimicrobial agents is an established risk factor for development of NTS diarrhea [31, 33]. Prior antimicrobial use and malnutrition contribute to abnormal gastrointestinal flora with possible loss of mucosal integrity.

***Malaria and anemia.*** Malaria has long been suspected to increase the risk of invasive NTS infection and might contribute to the seasonality of NTS disease. Although the mechanism underlying the association between malaria and NTS is only partially understood, malarial hemolysis may lead to impaired macrophage and neutrophil function due to the accumulation of malarial pigment by phagocytic cells, saturation of iron-binding proteins, and increased iron availability to NTS, a siderophilic organism. Although some studies have shown an association between malaria and NTS bacteremia [5], others have demonstrated an association between recent malaria or malarial anemia and NTS, compared with other causes of bacteremia [7, 15, 34]. Thus, measures directed at malaria control may have the potential to lead to reduction in the incidence of invasive NTS disease in tropical Africa.

***Malnutrition.*** Malnutrition was associated with NTS bacteremia among children in Kilifi, Kenya [4, 7]. Malnutrition, measles, and diarrheal disease were common reasons for admission to the hospital among children who subsequently developed hospital-acquired NTS disease in Rwanda [17]. Although children aged <3 years are at greater risk for NTS disease, those aged <4 months appear to be relatively protected, perhaps both by maternal antibodies [35] and by exclusive breast-feeding, which provides colostrum and limits exposure to unsafe water and food.

***HIV infection.*** NTS bacteremia is more common among HIV-infected individuals [2, 29], and the association with HIV infection is strongest among adults. Recurrent NTS bacteremia is a World Health Organization (WHO) stage 4 defining condition. Prophylactic therapy with trimethoprim-sulfamethoxazole is recommended to prevent the occurrence of opportunistic infections among HIV-infected patients [36]. This strategy appears to remain effective even in areas with high levels of resistance to trimethoprim-sulfamethoxazole among pathogens such as NTS [37]. Combination antiretroviral therapy has been associated with dramatic reductions in the incidence of NTS diarrhea and NTS bacteremia among HIV-infected persons in developed countries [38]. HIV infection is also a risk factor for bacteremia among children, including NTS bacteremia. HIV was associated with any bacteremia among children in Kilifi, Kenya (odds ratio, 3.22; 95% confidence interval, 2.34–4.44) and with NTS bacteremia (odds ratio, 3.21; 95% confidence interval, 1.95–5.28) [4].

***Gastric acid suppression.*** Use of medications that reduce gastric acidity is associated with an increased risk of gastrointestinal infection [39]. Infants have relative gastric achlorhydria, compared with adults, which may contribute to their risk of NTS disease.

***Sickle cell disease.*** Persons homozygous for sickle cell disease are at particular risk for bacterial sepsis, including NTS bacteremia. Of 78 consecutive cases of acute osteomyelitis complicating sickle cell disease in Nigeria involving patients with a mean age of 12 years (range, 9 months-50 years), 32 were able to have culture of blood or pus performed and one-half of the cases were due to *Salmonella* species [16].

***Schistosomiasis.*** Intestinal schistosomiasis may be a risk factor for invasive NTS disease among children in areas of endemicity [40]. However, among HIV-infected adults in Malawi, the presence of intestinal helminths was not shown to be associated with NTS bacteremia [41].

## CLINICAL PRESENTATION AND DIAGNOSIS

Fever or sweats were noted among 95% and splenomegaly among 38% of 100 Malawian adults at initial presentation with NTS bacteremia, features that are also seen in malaria. The median hemoglobin level in this group, 99% of whom were HIV infected, was 6.8 g/dL (range, 2.5–11.7 g/dL) [11]. Fever and splenomegaly predicted NTS bacteremia among hospitalized adults in Malawi [42]. In Tanzania, patients admitted to the hospital for antimalarial treatment were more likely to die when the results of a malaria slide test were negative than when the results were positive [43], which suggests that a lack of capacity to diagnose and treat nonmalarial infections, such as bacterial sepsis, may contribute to outcome. Among 166 children with NTS bacteremia in Kenya, splenomegaly was present in 44% and fever in 94% [7]. In the same rural district, 26% of all inpatient childhood deaths were associated with bacteremia, whereas 22% of such deaths were associated with malaria. Of children with malaria who died, 21% also had bacteremia [4].

NTS bacteremia frequently occurs without gastrointestinal symptoms in adults [11] and children [7]. Peters et al [42] have noted that, although pneumococcal or mycobacterial sepsis in adult patients could often be diagnosed clinically before blood culture results became available, NTS sepsis was much more difficult to diagnose on clinical grounds, because of nonspecific symptoms and signs. The syndrome of childhood pneumonia overlaps with both malaria and NTS sepsis [7, 15, 17]. Because clinical diagnosis of NTS bacteremia is difficult, blood culture facilities are needed to diagnose it and to conduct accurate surveillance to guide public health policy. Unfortunately, adequate clinical laboratory infrastructure is frequently lacking in resource-poor countries in Africa [44].

Outcomes were studied among 100 Malawian adults with NTS bacteremia, 99% of whom were HIV infected; 47% died within 1 month and 77% died within 1 year after the index presentation, and 43% of the initial survivors experienced at least 1 recurrence of NTS bacteremia. Molecular testing revealed that recurrence was due to recrudescence, rather than reinfection, in most instances [11]. Recrudescence probably occurs because of persistence of NTS intracellularly in the reticuloendothelial system.

## CLINICAL MANAGEMENT

Empirical treatment of childhood sepsis in accordance with WHO guidelines [45], with penicillin and chloramphenicol or ampicillin and gentamicin, may not provide adequate coverage for NTS disease that is resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. Gentamicin has limited activity against intracellular pathogens, so although isolates may appear susceptible in vitro, gentamicin cannot be relied on in vivo. WHO guidelines advise that, when there is known substantial antimicrobial resistance to traditional first-line antimicrobial agents, use of a third-generation cephalosporin may be appropriate [45]. The cerebrospinal fluid penetration of ceftriaxone makes it a good choice for treatment of meningitis. A recent report on pediatric NTS meningitis from Malawi during 1997–2006 demonstrated a static case-fatality rate of ~50% but a decrease in permanent sequelae over time, possibly associated with a change in duration of therapy from 2 to 4 weeks [46]. The Centers for Disease Control and Prevention recommends ciprofloxacin for the treatment of NTS bacteremia in HIV-infected adults, given for 4–6 weeks if the CD4 cell count is <200 cells/$mm^3$, followed by long-term secondary prophylaxis [47]. Data to guide duration of therapy or secondary prophylaxis for neonates, patients with meningitis, and HIV-infected persons in Africa are lacking. *Salmonella* serotype Typhi with decreased ciprofloxacin susceptibility, often associated with nalidixic acid resistance, may not respond adequately to ciprofloxacin therapy. It is not known whether this is also true for NTS [48]. When patients with NTS bacteremia do not respond to appropriate antimicrobial therapy, a search for focal disease and for schistosomiasis coinfection is warranted.

## MICROBIOLOGY

*S.* Typhimurium and *Salmonella* Enteritidis are the most common serotypes of NTS causing human disease in sub-Saharan Africa [7, 9, 10, 29, 35, 49]. The acquisition of a plasmid conveying a multidrug-resistant phenotype may be associated with successful spread and has been observed with *S.* Typhimurium in Malawi [10]. *Salmonella* Isangi was a rare serotype in South Africa until 2002, when it expanded to account for 20% of NTS isolates in a national surveillance program and was found to produce an extended-spectrum $\beta$-lactamase [50]. Antimicrobial resistance of NTS to trimethoprim-sulfamethoxazole, ampicillin, and chloramphenicol has become common in sub-Saharan Africa, which limits the value of these agents for management of invasive NTS [5, 10, 12, 17].

## NTS VACCINE PROSPECTS

The virulence of NTS is dependent on its ability to grow within macrophages of the reticuloendothelial system [51]. Extracellular replication and bacteremic dissemination also occur. Resistance to complement killing, by way of long-chain lipopolysaccharide, is an important virulence trait. Both complement and specific antibodies together are required to kill *Salmonella* species in vitro. Although serum samples from healthy African adults were able to kill NTS, serum samples from children aged <16 months often did not contain specific antibody titers sufficient to kill effectively [35]. This probably explains the predisposition of young children to invasive NTS disease and may go some way toward helping us understand a mechanism by which the immune dysregulation of HIV infection contributes to NTS disease risk. Such immunological clues suggest that vaccine development directed toward the common invasive serotypes could be a useful approach to prevent invasive NTS disease.

## CONCLUSIONS AND FUTURE DIRECTIONS

As invasive diseases caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* are controlled by vaccine strategies, invasive non-Typhi *Salmonella* disease may consolidate its position as a leading cause of community-acquired bloodstream infection in sub-Saharan Africa.

Despite the substantial burden of illness and death caused by invasive NTS disease, much remains to be done to understand and control invasive NTS disease in sub-Saharan Africa. A clearer understanding of the incidence, complications, and case-fatality rates at the population level would be valuable in deciding how to prioritize health care resources. A scale-up of access to blood culture or to improved alternative diagnostic methods is needed to support such studies, to improve patient care, and to inform policy. Research to determine the major environmental sources and modes of transmission and to characterize risk factors for mucosal colonization or infection and for invasive disease is urgently needed. It would be useful to understand more about the syndrome of invasive NTS in sub-Saharan Africa, including the proportion of persons with NTS diarrhea or NTS carriage who also develop invasive disease, the pathogenesis, the prevalence of carriage and chronic shedding, and the risk of NTS bacteremia attributable to comorbid conditions, such as malnutrition, malaria, and HIV infection. Algorithms for the management of febrile illness need to be continually reevaluated to address the relative importance of malaria versus invasive bacterial infections such as NTS. Clinical effectiveness studies and surveillance of antimicrobial resistance and serotype distribution are needed to inform clinical management strategies, to detect changes in patterns of disease, and to assist in vaccine development.


## Acknowledgments

***Financial support.*** US National Institutes of Health awards: AIDS International Training and Research Program, Fogarty International Center (D43 PA-03–018 to H.O.R. and J.A.C.), International Studies of AIDS-associated Co-infections (AI062563 to H.O.R. and J.A.C.), the Duke University Center for AIDS Research (AI64518 to H.O.R. and J.A.C.), and the Duke Clinical Trials Unit and Clinical Research Sites (AI069484–01 to J.A.C.); the Hubert-Yeargan Center for Global Health and a Duke Clinical Research Institute Synderman Award, Duke University Medical Center (to S.C.M.).

***Potential conflicts of interest.*** All authors: no conflicts.


## References


1. Brenner FW, Villar RG, Angulo FJ, Tauxe R, Swaminathan B. *Salmonella* nomenclature. J Clin Microbiol **2000**; 38:2465–7.
2. Shaw AV, Reddy EA, Crump JA. Etiology of community-acquired bloodstream infections in Africa [abstract L-620]. In: Program and abstracts of the 46th Annual Meeting of the Infectious Diseases Society of America (Washington, DC). Alexandria, VA: Infectious Diseases Society of America, **2008**.
3. Sigauque B, Roca A, Mandomando I, et al. Community-acquired bacteremia among children admitted to a rural hospital in Mozambique. Pediatr Infect Dis J **2009**; 28:108–13.
4. Berkley JA, Lowe BS, Mwangi I, et al. Bacteremia among children admitted to a rural hospital in Kenya. N Engl J Med **2005**; 352:39–47.
5. Enwere G, Biney E, Cheung YB, et al. Epidemiologic and clinical characteristics of community-acquired invasive bacterial infections in children aged 2–29 months in the Gambia. Pediatr Infect Dis J **2006**; 25: 700–5.
6. Gilks CF. Acute bacterial infections and HIV disease. Br Med Bull **1998**; 54:383–93.
7. Brent AJ, Oundo JO, Mwangi I, Ochola L, Lowe B, Berkley JA. *Salmonella* bacteremia in Kenyan children. Pediatr Infect Dis J **2006**; 25: 230–6.
8. Walsh AL, Phiri AJ, Graham SM, Molyneux EM, Molyneux ME. Bacteremia in febrile Malawian children: clinical and microbiologic features. Pediatr Infect Dis J **2000**; 19:312–8.
9. Graham SM, Walsh AL, Molyneux EM, Phiri AJ, Molyneux ME. Clinical presentation of non-typhoidal *Salmonella* bacteraemia in Malawian children. Trans R Soc Trop Med Hyg **2000**; 94:310–4.
10. Gordon MA, Graham SM, Walsh AL, et al. Epidemics of invasive *Salmonella enterica* serovar Enteritidis and *S. enterica* serovar Typhimurium infection associated with multidrug resistance among adults and children in Malawi. Clin Infect Dis **2008**; 46:963–9.
11. Gordon MA, Banda HT, Gondwe M, et al. Non-typhoidal *Salmonella* bacteraemia among HIV-infected Malawian adults: high mortality and frequent recrudescence. AIDS **2002**; 16:1633–41.
12. Milledge J, Calis JC, Graham SM, et al. Aetiology of neonatal sepsis in Blantyre, Malawi: 1996–2001. Ann Trop Paediatr **2005**; 25:101–10.
13. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ **2004**; 82:346–53.
14. Mweu E, English M. Typhoid fever in children in Africa. Trop Med Int Health **2008**; 13:532–40.
15. Graham SM, Molyneux EM, Walsh AL, Cheesbrough JS, Molyneux ME, Hart CA. Nontyphoidal *Salmonella* infections of children in tropical Africa. Pediatr Infect Dis J **2000**; 19:1189–96.
16. Ebong WW. Acute osteomyelitis in Nigerians with sickle cell disease. Ann Rheum Dis **1986**; 45:911–5.
17. Lepage P, Bogaerts J, Van Goethem C, Hitimana DG, Nsengumuremyi F. Multiresistant *Salmonella* Typhimurium systemic infection in Rwanda: clinical features and treatment with cefotaxime. J Antimicrob Chemother **1990**; 26(Suppl A):53–7.
18. Lavy CB, Thyoka M, Pitani AD. Clinical features and microbiology in 204 cases of septic arthritis in Malawian children. J Bone Joint Surg Br **2005**; 87:1545–8.

19. Martinson NA, Karstaedt A, Venter WD, et al. Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study. AIDS **2007**; 21:2043–50.
20. Oxford Centre for Evidence-based Medicine. Levels of evidence. Available at: http://www.cebm.net/index.aspx?o = 1025. Accessed 26 March 2009.
21. Torrey S, Fleisher G, Jaffe D. Incidence of *Salmonella* bacteremia in infants with *Salmonella* gastroenteritis. J Pediatr **1986**; 108:718–21.
22. Kariuki S, Revathi G, Kariuki N, et al. Invasive multidrug-resistant non-typhoidal *Salmonella* infections in Africa: zoonotic or anthroponotic transmission? J Med Microbiol **2006**; 55:585–91.
23. Wright RC. The seasonality of bacterial quality of water in a tropical developing country (Sierra Leone). J Hyg (Lond) **1986**; 96:75–82.
24. Mintz ED, Reiff FM, Tauxe RV. Safe water treatment and storage in the home: a practical new strategy to prevent waterborne disease. JAMA **1995**; 273:948–53.
25. Clasen T, Schmidt WP, Rabie T, Roberts I, Cairncross S. Interventions to improve water quality for preventing diarrhoea: systematic review and meta-analysis. BMJ **2007**; 334:782.
26. Crump JA, Griffin PM, Angulo FJ. Bacterial contamination of animal feed and its relationship to human foodborne illness. Clin Infect Dis **2002**; 35:859–65.
27. Schlundt J, Toyofuku H, Jansen J, Herbst SA. Emerging food-borne zoonoses. Rev Sci Tech **2004**; 23:513–33.
28. Centers for Disease Control and Prevention. Three outbreaks of salmonellosis associated with baby poultry from three hatcheries—United States, 2006. MMWR Morb Mortal Wkly Rep **2007**; 56:273–6.
29. Gordon MA. *Salmonella* infections in immunocompromised adults. J Infect **2008**; 56:413–22.
30. Nkuo-Akenji TK, Ntemgwa ML, Ndip RN. Asymptomatic salmonellosis and drug susceptibility in the Buea District, Cameroon. Cent Afr J Med **2001**; 47:254–7.
31. Paton S, Nicolle L, Mwongera M, et al. *Salmonella* and *Shigella* gastroenteritis at a public teaching hospital in Nairobi, Kenya. Infect Control Hosp Epidemiol **1991**; 12:710–7.
32. World Health Organization, Department of Communicable Disease, Surveillance and Response. Prevention of hospital-acquired infections: a practical guide. 2nd ed. Geneva: World Health Organization, **2002**. Available at: http://www.who.int/csr/resources/publications/drugresist/WHO_CDS_CSR_EPH_2002_12/en/. Accessed 4 January 2009.
33. Pavia AT, Shipman LD, Wells JG, et al. Epidemiologic evidence that prior antimicrobial exposure decreases resistance to infection by antimicrobial-sensitive *Salmonella*. J Infect Dis **1990**; 161:255–60.
34. Mabey DC, Brown A, Greenwood BM. *Plasmodium falciparum* malaria and *Salmonella* infections in Gambian children. J Infect Dis **1987**; 155: 1319–21.
35. MacLennan CA, Gondwe EN, Msefula CL, et al. The neglected role of antibody in protection against bacteremia caused by nontyphoidal strains of *Salmonella* in African children. J Clin Invest **2008**; 118:1553–62.
36. Provisional WHO/UNAIDS recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. Afr Health Sci **2001**; 1:30–1.
37. Watera C, Todd J, Muwonge R, et al. Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1-infected adults attending an HIV/AIDS clinic in Uganda. J Acquir Immune Defic Syndr **2006**; 42:373–8.
38. Hung CC, Hung MN, Hsueh PR, et al. Risk of recurrent nontyphoid *Salmonella* bacteremia in HIV-infected patients in the era of highly active antiretroviral therapy and an increasing trend of fluoroquinolone resistance. Clin Infect Dis **2007**; 45:e60–7.
39. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol **2007**; 102:2047–56.
40. Gendrel D, Kombila M, Beaudoin-Leblevec G, Richard-Lenoble D. Nontyphoidal salmonellal septicemia in Gabonese children infected with *Schistosoma intercalatum*. Clin Infect Dis **1994**; 18:103–5.
41. Dowling JJ, Whitty CJ, Chaponda M, et al. Are intestinal helminths a risk factor for non-typhoidal *Salmonella* bacteraemia in adults in Africa who are seropositive for HIV? A case-control study. Ann Trop Med Parasitol **2002**; 96:203–8.
42. Peters RP, Zijlstra EE, Schijffelen MJ, et al. A prospective study of bloodstream infections as cause of fever in Malawi: clinical predictors and implications for management. Trop Med Int Health **2004**; 9:928–34.
43. Reyburn H, Mbatia R, Drakeley C, et al. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ **2004**; 329:1212.
44. Petti CA, Polage CR, Quinn TC, Ronald AR, Sande MA. Laboratory medicine in Africa: a barrier to effective health care. Clin Infect Dis **2006**; 42:377–82.
45. World Health Organization. Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources. Geneva: World Health Organization, **2005**. Available at: http://www.helid.desastres.net/?e = d-000who-000-1-0-010-4-0-0-10l-11en-5000-50-about-0-01131-001-110utfZz-8-0-0&a = d&c = who&cl = CL4&d = Js13431e.10.5. Accessed 4 January 2009.
46. Molyneux EM, Mankhambo LA, Phiri A, et al. The outcome of nontyphoidal *Salmonella* meningitis in Malawian children, 1997–2006. Ann Trop Paediatr **2009**; 29:13–22.
47. Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. MMWR Recomm Rep **2004**; 53:1–112.
48. Crump JA, Barrett TJ, Nelson JT, Angulo FJ. Reevaluating fluoroquinolone breakpoints for *Salmonella enterica* serotype Typhi and for non-Typhi salmonellae. Clin Infect Dis **2003**; 37:75–81.
49. Galanis E, Lo Fo Wong DM, Patrick ME, et al. Web-based surveillance and global *Salmonella* distribution, 2000–2002. Emerg Infect Dis **2006**; 12:381–8.
50. Kruger T, Szabo D, Keddy KH, et al. Infections with nontyphoidal *Salmonella* species producing TEM-63 or a novel TEM enzyme, TEM-131, in South Africa. Antimicrob Agents Chemother **2004**; 48:4263–70.
51. Fields PI, Swanson RV, Haidaris CG, Heffron F. Mutants of *Salmonella* Typhimurium that cannot survive within the macrophage are avirulent. Proc Natl Acad Sci U S A **1986**; 83:5189–93.