Invasive non-Typhi *Salmonella* Disease in Africa

A Systematic Review

By
Habib Omari

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Approved by:

Advisor: William A. Sollecito, Dr PH.

Second Reader: Susan Moperth, MB, ChB, DTM & H

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ABSTRACT

Background:
Invasive non-Typhi Salmonella (NTS) infection is endemic in sub-Saharan Africa where it is the leading cause of blood stream infection. Host risk factors such as HIV infection, malaria and/or anemia, recent antimicrobial use, malnutrition, extreme ages, sickle cell disease and schistosomiasis have been reported in some studies. However, little information is available about environmental reservoir. Since a systematic review had not been done to assess if NTS infection is more likely to occur in persons with named risk factors compared to those without risk factors, preventive strategies are underdeveloped.

Objective:
The primary objective of this paper is to review the literature systematically and answer the questions whether NTS infection is associated with any of the following: HIV infection, malaria, recent antimicrobial use, anemia, sickle cell, schistosomiasis, malnutrition and extreme ages. The role of environment in the spread of NTS infection will also be explored.

Methods:
The systematic review was conducted by searching MEDLINE including the clinical queries option through December 2008 for English language articles containing the MESH phrases (Salmonella) NOT (Salmonella Typhi) NOT (Salmonella Enteric serovar) AND (Africa) OR (Sub-Saharan Africa). The articles that could not be retrieved from the
Medline were obtained from the CDC library. The search was also expanded using cited references from the articles obtained in the initial search.

**Results:**

Of 571 articles obtained, 93 were reviewed to yield 6 articles to find an association between NTS and the named risk factors. Moreover 9 articles explore the role of environment reservoir. NTS infection was significantly associated with HIV infection OR= 3.21 (95%CI 1.95-5.28), severe malnutrition OR= 2.2 (95%CI) and malaria OR=1.6. NTS infection was common in patients with sickle cell disease, schistosomiasis, extreme age and those with history of recent antimicrobial use but lacked statistical significance. Seasonal peaks of NTS disease occur during the rainy season among both adults and children suggesting environmental risk factors are important.

**Conclusions:**

Invasive NTS infection was associated HIV, Severe malnutrition and Malaria in Sub Saharan Africa. Because of the substantial burden of illness and death caused by invasive NTS disease, it is important to utilize these associations in developing preventive strategies to control invasive NTS infection in Sub Saharan Africa.
Glossary of terms

1. NTS = Non-Typhi Salmonella
2. Bacteremia = Bacteria in the blood stream
3. Osteomyelitis = Infection of the bone or bone marrow. Usually caused by pyogenic bacteria or mycobacteria
4. Pathogens = Disease causing organisms
5. Zoonotic = Animal diseases which can be transmitted to human such as rabies etc.
6. Nosocomial = Hospital acquired infections
7. Achlorydia = Absence or low production of gastric acid
8. Hemolysis = Destruction of red blood cells
9. Phagocytic cells = Cells that are responsible for engulfing and destroying foreign bodies
10. Siderophilic organisms = Iron loving organisms. They live by oxidizing iron.
11. Schistosomiasis= also known as bilharziasis or snail fever, is a primarily tropical parasitic disease caused by the larvae of one or more of five types of flatworms or blood flukes known as schistosomes
12. Splenomegaly = Enlarged spleen
13. In vitro = Technique of performing a procedure under controlled environment outside the organisms
14. In vivo = Technique of performing a procedure inside an organism
15. Virulence = Ability of the organism to infect another organism
16. SXT = Antibacterial combination of trimethoprim and sulphamethaxazole
17. Recrudescence = Reappearance of disease after it has been quiescent
1. INTRODUCTION

Salmonella enterica subspecies enterica includes over 2,400 serotypes found in humans and other warm-blooded animals. Non-Typhi Salmonella enterica serotypes are abbreviated using their serotype name, for example Salmonella Typhimurium [1]. Non-Typhi Salmonella (NTS) is among the three most common pathogens causing bacterial bloodstream infections in adults and children in sub-Saharan Africa [2-9]. HIV-infected adults and children <3 years of age carry most of the burden of invasive disease and mortality in these groups is high. This contrasts to the developed world, where NTS disease is usually a self-limited colitis, and mortality is low, even in immunosuppressed, young or elderly, bacteremic patients.

2. METHODS OF SYSTEMATIC REVIEW

2.1 Focused questions

A systematic review of the literature relative to NTS was carried out to address the following focused questions:

- Is the Invasive NTS more likely to occur in HIV infected patients than in uninfected persons?
- Is the Invasive NTS more likely to occur in people with Malaria and/or Anemia than those without Malaria and or Anemia?
- Is the invasive NTS more likely to occur in malnourished children than in those who are well nourished?
- Is Invasive NTS infection more likely to occur in people with recent history of antimicrobial than in those without recent history of antimicrobial use?
• Is Invasive NTS more likely to occur in people with extreme ages (<5 years and elders) than others?
• Is Invasive NTS more likely to occur in patients with sickle cell than in those without sickle cell disease?
• Is invasive NTS more likely to occur in patients with schistosomiasis than in those without schistosomiasis?
• What is the role of environment with regard to invasive NTS infection?

2.2. Data sources and search strategy
Utilizing the outline in Figure 1, the following data sources and search strategy was used. To identify relevant articles, a MEDLINE electronic database search using PubMed, was performed to explore the articles published from 1986 through 2008. The search was done in the English language. The following medical headings (MeSH) and key words were used in the search strategy: (Salmonella) NOT (Salmonella typhi )NOT (Salmonella enteric serovar) AND (Africa )OR (Sub-Saharan Africa). Specific terms used under overall search were bacteremia, sepsis, septicemia, fever, antimicrobial drug resistance, therapeutics, treatment, therapy, prophylaxis, epidemics, risk factors, malaria, HIV, environmental microbiology, water, water microbiology, water supply, prevention & control, prevention, primary prevention, guidelines, Health planning guidelines, practice guidelines, standards and guidelines. The articles that could not be retrieved from Medline were obtained from CDC library. The search process was then expanded by identifying additional articles from cited references in articles obtained in the initial search. The abstracts of these articles were examined with respect to inclusion criteria.
2.3. Inclusion criteria

The following were used as inclusion criteria:

- Publications from peer reviewed journals.
- Presentation and analysis of Non salmonella data from Africa and some other parts of developed world.

The abstracts of selected articles were reviewed to assess those which met eligibility criteria. The quality of each study was assessed using Oxford Centre for Evidence Based Medicine Levels of Evidence (May 2001 Version). Quality ratings of studies are shown (see table 1).

3. BURDEN OF DISEASE

Invasive NTS disease is endemic in sub-Saharan Africa, in both rural and urban areas. The burden of mortality from childhood invasive bacterial disease in sub-Saharan Africa is probably greater than that of malaria in many communities [5]. In rural Kenya, the estimated minimum incidence of bacteremia was 505 per 100,000 person-years in the under 5-years age group, of which 88 per 100,000 person-years was NTS bacteremia. In rural Mozambique childhood bacteremia incidence was 425 per 100,000 person-years in children <15 years of age, of which NTS incidence was 120/100,000 person-years [9]. The true incidence of bacteremia is likely to be 2-3 times this figure, as bacteremia among children dying before reaching the district hospital was unable to be ascertained in either study [5, 9]. While studying the impact of the conjugate pneumococcal vaccine in the Gambia, Enwere et al demonstrated an incidence of NTS
bacteremia of 262 per 100,000 person-years among children aged ≤ 29 months not vaccinated with the pneumococcal vaccine [6]. In Uganda, NTS bacteremia was reported to be rare among adults with CD4-positive T-lymphocyte counts (CD4 counts) above 500 cells/mm³, but 500 per 100,000 per year among adults with CD4 counts 200 to 500 cells/mm³, and 7,500 per 100,000 per year among adults with CD4 counts < 200 cells/mm³ [10]. Case fatality estimates for invasive NTS disease in Africa have ranged between 4.4% and 27% in children [6, 11-13] and between 22 and 47% in adults [8, 14]. Case fatality in meningitis may be higher with NTS than for any other common cause of bacterial meningitis. For example, in Malawi 64% of neonates with NTS meningitis died compared to 26% for group B *Streptococcus* meningitis [4]. While these studies provide some insight into the burden of invasive NTS disease for Africa, none are population-based and most have focused on high risk groups such as young children and HIV-infected adults. The actual incidence is likely to vary by population HIV prevalence, local conditions and age distribution. It is likely that the incidence of invasive NTS disease in sub-Saharan Africa is higher than for typhoid fever, which has been estimated to occur with an incidence of 50 per 100,000 per year in Africa [15]. Furthermore, hospital-based studies suggest that typhoid fever may be considerably less common than invasive NTS in sub-Saharan Africa [16].

Data on the frequency of complications of NTS bacteremia in Africa are limited. Meningitis, septic arthritis and osteomyelitis are described [3, 11, 17, 18], especially among children, where NTS may be more common than *Staphylococcus aureus* as a cause of septic arthritis [19]. Gordon et al investigated 100 adults in Malawi, 99% of whom were HIV-infected, with NTS bacteremia for focal suppurative disease and did not
identify any localized NTS infections at initial presentation [14]. Of 2,517 pediatric patients with NTS bacteremia in Blantyre, Malawi over 1998-2004, 85% were <36 months old and 19-35% were estimated to be HIV-infected [8]. During the same period 2,439 adults with NTS bacteremia were identified and approximately 95-98% of these patients were HIV-infected. A South African autopsy study of 50 patients who died with a pre-mortem clinical diagnosis of tuberculosis revealed that 94% were HIV-infected and 23% of these patients were harboring splenic NTS [20].

4.0. RISK FACTORS AND PREVENTION STRATEGIES

Risk factors for NTS infection in Africa have not been well characterized; consequently evidence-based prevention interventions are limited. Small African studies and evidence-based prevention studies for 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].

4.1. Environmental risk factors

4.1.1. Food and Water

Seasonal peaks of NTS disease occur with the rainy season among both adults and children [4, 8, 11, 22] suggesting that environmental risk factors are important. Fecal organisms are found at highest concentrations in drinking water sources in Africa at the onset of the wet season [23] and this may correspond with increased risk of waterborne
NTS. Protection of source water, increased access to central safe water, safe water storage in the home [24], and improved water quality at the household level are likely to reduce exposure to NTS and to other enteric pathogens [25]. Strategies such as use of narrow-mouthed, spigoted containers for water storage [26] and treatment of water at home by chlorination, solar disinfection, filtration, flocculation, or a combination of measures have been shown to reduce the risk for diarrhea [27]. Numerous outbreaks of food-borne illness due to NTS have been studied in industrialized countries and such outbreaks have also 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 disease to humans in developed countries [28]. NTS have 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 utilized in developing as well as industrialized countries to improve food safety and to control NTS [29].

4.1.2. Zoonotic and anthroponotic transmission

Animal contact, particularly handling of young chickens by children, is a well-established risk factor for acquisition of NTS disease in industrialized countries [30]. While not often considered a common risk factor for NTS infection in developed world studies, anthroponotic transmission has been suggested as being relatively more important in Africa [22, 31]. Kariuki et al demonstrated carriage of identical strains of NTS in the stool of human household contacts of pediatric cases of invasive disease,
and a lack of such strains from environmental and domestic animal sampling from the households, although a common source from food or water could not be ruled out [22]. Asymptomatic carriers of NTS have been demonstrated in Africa [32]. A Kenyan study of NTS carriage at admission to hospital found that 20 (3.6%) of 556 children were carriers but none of 111 adults carried NTS [33]. Asymptomatic carriers of NTS have also been described in more developed countries, where it is known that children are likely to excrete NTS in their stool for some weeks after recovering from enteric infection.

4.1.3. Nosocomial transmission

Outbreaks of NTS have been described in hospitals in many parts of the world, occurring among patients admitted with a different diagnosis. Nosocomial outbreaks can be particularly severe on pediatric wards in developing countries where children may be malnourished and have other host risk factors. Transmission may be person-to-person, or from contaminated food. High case fatality is frequently observed especially when such outbreaks are caused by strains of NTS resistant to the local empiric therapy [18]. Ten percent of 360 adult and pediatric patients with nosocomial diarrhea occurring in a Kenyan hospital in 1988 were due to Salmonella. Among children recent antimicrobial use, age 6 months to 6 years, and crowded living conditions at home were associated with nosocomial diarrhea due to Salmonella. Among adults, sharing a hospital room with somebody with diarrhea and a history of previous hospitalization were associated with nosocomial Salmonella diarrhea [33]. Prevention strategies could include patient and visitor education regarding personal hygiene and food preparation and storage (in
African hospitals food is usually provided by a patient’s family), provision of safe
drinking water, hand washing before and after patient contact by healthcare workers,
thorough cleaning of the hospital environment, reduction in crowding, avoiding sharing
beds between children, increasing the number of healthcare workers, adequate
disinfection of reusable equipment, and surveillance for NTS infections and isolation of
identified cases [18, 34].

4.2. Host risk factors

4.2.1. Age

Children and infants under the age of 3 years are particularly at risk for invasive NTS
disease. Infants have less well developed immune systems and relative gastric
achlorydia compared with adults [6]. Endovascular infections with NTS are described in
adults >50 years of age in the industrialized world. Older age may also be a risk factor
in African populations, but is dominated by HIV-associated NTS disease among
younger adults.

4.2.2. Exposure to antimicrobials

Recent use of antimicrobial agents, is an established risk factor for development of NTS
gastrointestinal infection [35]. Among children in a Kenyan hospital in 1988, recent
antimicrobial use was associated with nosocomial diarrhea due to Salmonella [33]. Prior
antimicrobial use and malnutrition contribute to abnormal gastrointestinal flora with
possible loss of mucosal integrity. Use of an antimicrobial agent to which circulating
NTS are resistant could select for more resistant strains as well as interrupting the protective effect of normal intestinal flora.

4.2.3. Malaria and anemia

Malaria has long been suspected to increase the risk of invasive NTS infection and may contribute to the seasonality of NTS disease. While 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. While some studies have shown an association between malaria and NTS bacteremia [6], others have demonstrated an association between recent malaria or malarial anemia and NTS compared to other causes of bacteremia [3, 11, 36]. Thus measures directed at malaria control may have the potential to lead to reduction in invasive NTS disease in tropical Africa.

4.2.4. Malnutrition

Malnutrition was associated with NTS bacteremia among children in Kilifi, Kenya [5, 11]. Malnutrition, measles and diarrheal disease were common reasons for admission among children who subsequently developed nosocomial NTS disease in Rwanda [18]. While children < 3 years of age are at greater risk for NTS disease, those < 4 months old appear to be relatively protected, perhaps both by maternal antibody [37] and exclusive breast-feeding which provides colostrum and limits exposure to unsafe water and food.
4.2.5. HIV

NTS bacteremia is more common among HIV-infected individuals [2] and the association with HIV infection is strongest among adults. Recurrent NTS bacteremia is a WHO Stage 4 defining condition for patients with HIV. Prophylactic trimethoprim-sulfamethoxazole (SXT) is recommended to prevent the occurrence of opportunistic infections among HIV-infected patients in Africa [38]. This strategy appears to remain effective, even in areas with high levels of resistance to SXT among pathogens such as NTS [39]. Combination antiretroviral therapy has been associated with dramatic reductions in the incidence of NTS enteritis and NTS bacteremia among HIV-infected persons in the developed world [40]. 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, OR 3.22 (95% CI 2.34–4.44) and with NTS bacteremia, OR 3.21 (95% CI 1.95-5.28) [5].

4.2.6. Gastric acid suppression

Use of medications that reduce gastric acidity is associated with increased risk of gastrointestinal infection [41].

4.2.7. Sickle Cell Disease

Persons homozygous for sickle cell disease are particularly at risk for bacterial sepsis, including NTS bacteremia. Among 78 consecutive cases of acute osteomyelitis complicating sickle cell disease in Nigeria, with a mean age of 12 years (range 9
months – 50 years), 32 were able to have cultures of blood or pus performed and half the cases were due to *Salmonella* [17].

4.2.8. *Schistosomiasis*

Intestinal schistosomiasis may be a risk factor for acquisition of invasive NTS disease among older children in endemic regions [42]. However, among HIV-infected adults in Malawi, the presence of intestinal helminths was not shown to be associated with NTS bacteremia [43].

5. CLINICAL PRESENTATION AND DIAGNOSIS

Fever or sweats were noted among 95% of 100 Malawian adults and splenomegaly among 38% at initial presentation with NTS bacteremia, features suggestive of malaria in Africa. The median (range) hemoglobin in this 99% HIV-infected group was 6.8g/dL (2.5 – 11.7g/dL) [14]. Fever and splenomegaly predicted NTS bacteremia among hospitalized adults in Malawi [7]. In Tanzania, patients admitted to hospital for antimalarial treatment were more likely to die if their malaria slide was negative than if it was positive [44], suggesting that a lack of capacity to diagnose and treat other causes of fever such as bacterial sepsis may contribute to outcome. Among 166 children with NTS bacteremia in Kilifi, Kenya, splenomegaly was present in 44% of cases, fever in 94% [11]. 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 patients dying with malaria, 21% were also bacteremic [5].
NTS bacteremia frequently occurs without gastrointestinal symptoms in adults [14] and children [11]. Peters et al have noted that while adult patients with pneumococcal or mycobacterial sepsis could often be diagnosed clinically prior to blood culture results becoming available, patients with NTS sepsis were much more difficult to diagnose on clinical grounds due to nonspecific symptoms and signs [7]. The syndrome of childhood pneumonia overlaps with both malaria and NTS sepsis [3, 11, 18]. Because clinical diagnosis of NTS bacteremia is difficult, blood culture facilities are needed to diagnose invasive NTS and to conduct accurate surveillance to guide public health policy. Unfortunately adequate clinical laboratory infrastructure is frequently lacking in resource-poor countries in sub-Saharan Africa [45].

Outcomes were studied among Malawian adults with NTS bacteremia, 99% of whom were HIV-infected. Among 100 adults, 47% died within one month, 77% died within a year of their index presentation, and 43% of initial survivors developed at least one recurrence of NTS bacteremia. Molecular testing revealed that recurrence was due to recrudescence rather than reinfection in most instances [14]. Recrudescence probably occurs due to persistence of NTS intracellularly in the reticuloendothelial system.

6. CLINICAL MANAGEMENT

Empiric treatment of childhood sepsis according to World Health Organization (WHO) guidelines [46] with penicillin and chloramphenicol or ampicillin and gentamicin does not provide adequate cover for NTS disease that is resistant to ampicillin, SXT, and chloramphenicol. Gentamicin has limited activity for intracellular pathogens, so even though isolates may appear susceptible in vitro, the drug cannot be relied upon in vivo.
WHO guidelines advise that where there is known substantial antimicrobial resistance to traditional first-line antimicrobials, use of a third-generation cephalosporin may be appropriate [46]. The CSF penetration of ceftriaxone makes it a good choice for meningitis. A recent report on pediatric NTS meningitis from Malawi over 1997-2006 demonstrated a static case fatality rate of approximately 50% but a fall in permanent sequelae over time, possibly associated with a change in duration of therapy from two to four weeks [47]. CDC recommends ciprofloxacin for the treatment of NTS bacteremia in HIV-infected adults and adolescents, for 4-6 weeks if the CD4 count is <200cells/mm³, followed by long-term secondary prophylaxis [48]. Data to guide duration of therapy or secondary prophylaxis for neonates, meningitis cases and HIV-infected persons in Africa is lacking. S. 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 [49]. When patients with NTS bacteremia do not respond to appropriate antimicrobial therapy a search for focal disease and for schistosomiasis co-infection is warranted.

7. MICROBIOLOGY

S. Typhimurium and S. Enteritidis are the most common serotypes of NTS causing human disease in sub-Saharan Africa [8, 11, 13, 31, 37, 50]. The acquisition of a plasmid conveying a multidrug resistant (MDR) phenotype may be associated with successful spread as has been observed with S. Typhimurium in Malawi [8]. S. Isangi was a rare serotype in South Africa until 2002 when it expanded to account for 20% of
NTS isolates from national surveillance and was found to produce an extended-
spectrum $\beta$-lactamase (ESBL) [51].
Antimicrobial resistance of NTS to SXT, ampicillin and chloramphenicol has become
common in sub-Saharan Africa limiting the value of these agents for management of
invasive NTS [4, 6, 8, 18].

8. NTS VACCINE PROSPECTS
Virulence of NTS is dependent on ability to grow within macrophages of the
reticuloendothelial system [52]. Extracellular replication and bacteremic dissemination
also occurs. Resistance to complement killing, by way of long chain lipopolysaccharide,
is an important virulence trait. Both complement and specific antibody together are
required to kill *Salmonella* in vitro. While healthy African adult serum was able to kill
NTS, serum from children <16 months of age often did not contain sufficient specific
antibody titres to kill effectively [37]. This probably explains the predisposition of young
children to invasive NTS disease and may go some way towards understanding a
mechanism by which the immune dysregulation of HIV infection contributes to NTS
disease risk. Such immunologic clues suggest that vaccine development directed
towards the common invasive serotypes could be a useful approach to control invasive
NTS disease.

9. DISCUSSION
The systematic review represent a novel attempt to rigorously assess the link between
Invasive non-Typhi salmonella infection and HIV, malaria, severe malnutrition, recent
microbial use, schistosoma and sickle cell disease in Sub-Saharan Africa. Lack of evidence in both quality and quantity failed to demonstrate outstanding association between schistosoma, sickle cell, age, recent antimicrobial use and invasive NTS infection. Our results however showed convincing association between HIV, severe malnutrition, malaria and invasive NTS infection.

There were notable studies that did not meet eligibility criteria (lack of rigor to be conclusive), but the trend of these studies is consistent with the findings of those studies which met criteria.

9.1. HIV infection and Invasive NTS infection

Two studies [5,40] have addressed the relationship between HIV and NTS bacteremia. Berkley AJ et al demonstrated that HIV infection is the risk factor for any bacteremia among children, including Invasive NTS infection. More specifically they showed that HIV infection was associated with invasive NTS infection among children in Kilifi Kenya, OR 3.22 (95% CI 2.34-4.44). An indirect association between HIV infection and NTS infection was shown by Hung CC et al [40]. In this study they showed that the incidence of Invasive NTS infection was reduced among HIV infected patients receiving anti-retroviral therapy. The mechanism of the association between HIV infection and NTS infection is clearly understood. HIV infection reduces individual immunity against infection and therefore keeps the person at risk of acquiring infection including but not limited to invasive NTS infection. Although the association between HIV infection and invasive NTS infection was demonstrated in cross-sectional epidemiologic surveys, the measurements of infections were done by state of the art equipments. In addition, HIV
was a recognized risk factor of Invasive NTS infection in developed countries [53]. Therefore these results are consistent with the results of other studies done outside Africa.

### 9.2. Severe Malnutrition and Invasive NTS infection

Two studies [5,11] have addressed the relationship between severe malnutrition and Invasive NTS infection. Berkley AJ et al [5] demonstrated that severe malnutrition is the risk factor for Invasive NTS infection. Malnutrition was among the commonest reason for admission among children with Invasive NTS infection. The odds of having Invasive NTS infection for children with severe malnutrition was 2.2 times higher than children without severe malnutrition. Brent AJ et al [11] also showed a positive association between severe malnutrition and Invasive NTS infection. In their study they showed that severe malnutrition is the risk factor for Invasive NTS disease OR 1.7(95%CI 1.2 - 2.4)

The nutritional requirements of the human body reflect the nutritional intake necessary to maintain optimal body function and to meet the body’s daily energy needs. Malnutrition (literally, "bad nutrition") is defined as "inadequate nutrition," and while most people interpret this as under-nutrition, falling short of daily nutritional requirements, it can also mean over-nutrition, meaning intake in excess of what the body uses. However, under-nutrition affects more than one-third of the world's children, and nearly 30 percent of people of all ages in the developing world, making this the most damaging form of malnutrition worldwide [54]. In fact, the relationship between malnutrition and infection is cyclical— infection predisposes one to malnutrition, and malnutrition, which impairs all immune defenses, predisposes one to infection.
9.3 Malaria/anemia and Invasive NTS infection

One study [6] has shown an association between malaria and Invasive NTS infection. Enwere G et al [6] have shown that patients with malaria are more likely to succumb to Invasive NTS infection than those without malaria. In another study Brent AJ et al [11] have shown that three-fourths of invasive NTS patients with anemia had evidence of either current or recent malaria. It was not possible to know which proportions of anemia was in fact due to malaria and therefore we can’t establish a temporal association between malaria and invasive NTS disease. Since malaria is a short term infection, prospective studies to ascertain temporal relationship are not feasible.

The mechanism underlying the association between malaria and invasive NTS infection is partially understood. Hemolysis caused by Malaria parasites may impair macrophage and neutrophil function due to accumulation of malarial pigment by phagocytic cells, saturation of iron binding proteins and increased iron availability to NTS, a siderophilic organism.

9.4 Recent antimicrobial use and Invasive NTS infection

There was no African study that established recent antimicrobial use is a risk factor of Invasive NTS infection. There is however one evidence from USA study that has established that association. Pavia AT et al [35] have shown that people who have been treated with antibiotics frequently develop infections of Salmonella bacteria that have become resistant to antibiotics because they have survived previous antibiotic treatment. Another suggested mechanism of this association is due to the fact that
frequent antimicrobial use disrupts intestinal mucosa integrity thereby enhancing microbial penetration though gut mucosa.

9.5 Age and Invasive NTS infection
We have not been able to show a temporal association between age and acquisition of Invasive NTS infection. However one of the African study [29] in an attempt to develop vaccine against NTS showed that Healthy African adult serum did kill *Salmonellae* unlike serum from children under the age of 16 months, which often did not contain sufficient specific antibody titres to kill effectively. This suggests that infants are more likely to suffer from NTS infection than adults. Besides having underdeveloped immune system, infants have less achlorydia compared to adults. Older age may also be a risk factor of Invasive NTS infection due to impaired immunity.

9.6 Schistosoma and Invasive NTS infection
There was one study [42] which linked schistosomiasis and Invasive NTS infection. Gendrel et al showed that *Schistosoma intercalatum* has been demonstrated from rectal biopsy in 48 (91%) of 53 children with invasive NTS infection compared to 21 (38%) of 55 in the control group (*P* <0.001), although only 28 of the controls had blood cultures performed. We can’t rely on this finding since only half of the controls have blood cultures performed. If all controls would have their blood cultures done and happen to have NTS, the results would be biased towards the null.

9.7 Sickle cell and Invasive NTS infection
There was no study that demonstrates an association between sickle cell disease and Invasive NTS infection. There was one study [17] which showed that Salmonella accounts for 50% of the 36 organisms isolated from 32 sickle cell patients co infected with osteomyelitis.

10. CONCLUSIONS AND FUTURE DIRECTIONS

As \textit{Streptococcus pneumoniae} and \textit{Haemophilus influenzae} invasive disease are controlled by vaccine strategies, invasive \textit{Salmonella} 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, more research needs to be done to understand and control invasive NTS in sub-Saharan Africa. Malaria, HIV and Severe Malnutrition have been associated with Invasive NTS infection. Since most of the febrile ill patients in Africa are diagnosed as having Malaria, it is crucial to improve our diagnostic technique and manage patients appropriately. This may involve increase in health expenditure by in country health ministries. Moreover, efforts directed to improve malaria control would be beneficial. Under-nutrition is the disease of the poor. Malnourished children are more likely to suffer from many infections than well nourished children. African Governments should make efforts to reduce poverty. This may be affected by combating corruption and explore employment opportunities. Research to determine the major environmental sources, modes of transmission, and to characterize risk factors for either 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.
Specifically to analyze further proportion of persons with NTS diarrhea, or NTS carriers who develop invasive disease, pathogenesis, and the mortality of NTS bacteremia attributable to co-morbid 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 for 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.

Improvement of diagnostic technique is crucial in order to prevent deaths associated with NTS bacteremia. Most importantly, clinical effectiveness studies and surveillance for antimicrobial resistance are needed in order to address clinical management strategies, to detect changes in the pattern of diseases and to assist in vaccine development.
Table 1. Classification of studies according to Oxford Evidence Based Medicine Levels of evidence (May 2001 version)

<table>
<thead>
<tr>
<th>STUDY TYPE</th>
<th>EBM LEVEL</th>
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<tbody>
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<td><strong>Food and Water</strong></td>
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<td>1b</td>
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<td>Wright 1986, Momba 2002</td>
<td>2c</td>
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<td>Clasen 2007</td>
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<td>Mintz 1995</td>
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<td><strong>Zoonotic and Anthroponotic transmission</strong></td>
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<td>Morbidity Mortality Weekly Report 2007</td>
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<td>Kariuki 2006</td>
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<td><strong>Nosocomial Transmission</strong></td>
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<td>Lepage 1990. Multiresistant Salmonella</td>
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<td><strong>Risk factor studies</strong></td>
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<td><strong>Age</strong></td>
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<td>Cohen et al.</td>
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<td><strong>Prior antimicrobial use</strong></td>
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<td>Pavia 1990. Antimicrobial exposure decrease resistance</td>
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<td><strong>Malaria and anemia</strong></td>
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<td>Enwere 2006 and Mabey 1987 et al</td>
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<td>Graham 2006, Bent</td>
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<td><strong>Malnutrition</strong></td>
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<td><strong>Gastric suppression</strong></td>
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<td>Leonard 2007</td>
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<td><strong>Schistosomiasis and sickle cell disease</strong></td>
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<td>Gendrel 1994 and Dowling 2002.</td>
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<td>Ebong 1986</td>
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Figure 1. Literature review.

Citations identified by initial search
N= 571

Articles retrieved for in depth review N= 93

Articles not matching criteria N= 478

Articles reviewed from in depth review N= 11

Articles from CDC library N= 17

Articles not matching criteria N= 6

Articles meeting criteria N=15

Articles not meeting criteria and excluded N= 89

Articles associating risk factors and NTS N= 6

Articles associating environment and NTS N= 9
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