Invasive Infections with Nontyphoidal Salmonella in Sub-Saharan Africa

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ABSTRACT Invasive nontyphoidal Salmonella (NTS) infections in Africa cause an enormous burden of illness. These infections are often devastating, with mortality estimated at 20%, even with appropriate antimicrobial therapy. Two major groups—young children and HIV-infected adults—suffer the great majority of these infections. In children, younger age itself, as well as malaria, malnutrition, and HIV infection, are prominent risk factors. In adults, HIV infection is by far the most important risk factor. The most common serotypes in invasive infections are Salmonella enterica serotypes Typhimurium and Enteritidis. In recent years, a specific strain of Salmonella Typhimurium, multilocus sequence type 313, has caused epidemics of invasive disease. Little is known about risk factors for exposure to NTS, making the design of rational interventions to decrease exposure difficult. Antimicrobial therapy is critically important for treatment of invasive NTS infections. Thus, the emergence and spread of resistance to agents commonly used for treatment of invasive NTS infection, now including third-generation cephalosporins, is an ominous development. Already, many invasive NTS infections are essentially untreatable in many health care facilities in sub-Saharan Africa. Several candidate vaccines are in early development and, if safe and effective, could be promising. Interventions to prevent exposure to NTS (e.g., improved sanitation), to prevent the occurrence of disease if exposure does occur (e.g., vaccination, malaria control), and to prevent severe disease and death in those who become ill (e.g., preserving antimicrobial effectiveness) are all important in reducing the toll of invasive NTS disease in sub-Saharan Africa.

INTRODUCTION AND DISEASE BURDEN

Worldwide, Salmonella infection typically causes gastroenteritis and rarely causes invasive infections of normally sterile sites. A well-known exception is enteric fever (invasive infection caused by Salmonella enterica serotypes Typhi, Paratyphi A, Paratyphi B, or Paratyphi C), a syndrome of acute febrile illness, often with abdominal pain, headache, and other manifestations. However, nontyphoidal Salmonella (NTS) serotypes can also cause invasive infections, which often present as sepsis rather than as typical enteric fever (1). Vulnerable populations, such as infants, young children, and immunocompromised people of any age, are at risk. Invasive NTS infections in Africa cause an enormous burden of illness—Africa is estimated to account for more than half of the 3.4 million invasive NTS infections (2)—and these infections are often devastating, with a mortality rate estimated at 20% in African settings (3), even with appropriate antimicrobial therapy. Although invasive NTS infection has been recognized for decades as an important cause of invasive bacterial infection in sub-Saharan Africa, until recently it received relatively little attention (4, 5). However, this is changing, with increasing attention from the scientific community and...
from both governmental and nongovernmental organizations focused on understanding the sources of these infections and developing effective tools for prevention (4, 6).

The diagnosis of NTS infection relies on microbiological testing, typically culture of stool, blood, or other clinical specimens. The capacity to conduct such testing is unavailable in much of Africa (7, 8). Consequently, population-based surveillance information on the incidence of invasive NTS infections is also limited. Much of what is known comes from studies conducted in health care facilities or relatively small geographic areas that have enhanced microbiologic capacity, often developed to support research studies on other topics. For example, important information about invasive NTS infections has emerged from research programs on vaccine-preventable diseases, HIV infection, malaria, and other infectious diseases.

In many areas of sub-Saharan Africa, NTS is now recognized as the most common cause of community-acquired invasive bacterial infection, with an estimated overall incidence of 227 cases per 100,000 population annually (3). To some extent, this reflects the successful implementation of childhood vaccination for *Streptococcus pneumoniae* and *Haemophilus influenzae* in many countries, with great reductions in the burden of childhood invasive infections caused by these pathogens (4). However, the prominence of invasive NTS infection is not simply due to control of other infections. Early in the HIV epidemic, it became clear that invasive NTS infection was a common opportunistic infection in immunocompromised HIV-infected people throughout the world; the high prevalence of HIV in sub-Saharan Africa has contributed greatly to the high incidence of invasive NTS disease in the region. However, the incidence of invasive NTS disease varies substantially from place to place and time to time. For example, incidence rates exceeding 2,000 per 100,000 children under 5 years old per year have recently been reported in rural Kenya (9, 10), whereas in Mozambique in the same time frame, incidence was an order of magnitude lower, at just over 200 cases per 100,000 infants (11).

*Salmonella* is well known as a cause of outbreaks, some of which can extend over months or years. Because much of the information from Africa comes from point-in-time studies, rather than from ongoing disease surveillance, and because outbreak detection and investigation is limited, it is not clear what proportion of NTS infections are outbreak-associated, as opposed to sporadic. However, there are suggestions that outbreak-type dynamics may be driving the epidemiology of invasive NTS disease, at least to some extent. It is certainly clear that large, sustained outbreaks have occurred, because investigators in Malawi have documented serial outbreaks of invasive NTS disease caused by NTS of different serotypes and antimicrobial resistance patterns (12, 13), and investigators in Mali have documented a large, sustained outbreak caused by *Salmonella Enteritidis* (14). Similarly, in areas of Kenya that previously experienced the highest rates of invasive NTS disease ever reported (9), a recent report shows decreasing—although still very high—incidence from 2009 to 2014 (15). Progressive declines in annual incidence have also been reported in children in Mozambique and Malawi (11, 16). In the absence of other interventions or events that would have led to decreasing incidence, these observations suggest that large outbreaks or even a continent-wide epidemic may be or may have been responsible for a substantial part of the large burden of invasive NTS disease.

This chapter reviews the current state of knowledge on invasive NTS infections in Africa, focusing on epidemiologic aspects of these infections and opportunities for prevention while also addressing microbiologic aspects. Much is not known regarding the sources and transmission of these infections, and thus the ability to prevent them is hampered. However, prevention is much needed, because these infections are not only common and serious, but emerging antimicrobial resistance makes them increasingly difficult to treat.

**CLINICAL FEATURES AND RISK FACTORS**

Like most infectious diseases, invasive NTS infections can range from mild to severe. Because most studies have been conducted among inpatients, the published descriptions of clinical features lean toward the more severe end of the clinical spectrum. However, all indications are that, as in other settings, two major groups—young children and HIV-infected adults—suffer the greatest majority of these infections. It is also clear that mortality is substantial, typically around 20% in populations with standard access to medical services (12). In studies focused only on inpatients, mortality can exceed 50%, but even in community-based studies that include less severe illnesses that might not otherwise come to medical attention, mortality is in the 2 to 5% range (9).

**Invasive NTS Infection in Children**

In children, invasive NTS infections often present with a nonspecific febrile or toxic picture. Estimates of the proportion of patients with a history of antecedent...
diarrhea vary from about a quarter to a half (11, 17–19). In children for whom diarrhea is not reported, it is not clear whether relatively mild diarrhea might have occurred, but it is clear that many children do not present with the prominent bloody diarrhea often associated with severe enteric Salmonella infection. Indeed, many children present with respiratory symptoms that may even meet criteria for acute lower respiratory tract infection (17, 19–21). Most children have a septic picture, with positive blood cultures, but a small proportion have invasive focal infections, including meningitis, abscesses, osteomyelitis, septic arthritis, thoracic empyema, and even panophthalmitis (17, 22). Reported mortality has ranged widely, from about 3 to 20%, likely reflecting both variation in study methods, as discussed above, and the availability of effective antibiotics and other care.

Regardless of the overall case fatality ratio, however, multiple studies have shown that infants are more likely to die than older children (12, 23–25). Children who survive occasionally experience recrudescent disease, but this occurs less frequently in children than in adults. Aside from any other immunocompromising factors, and consistent with patterns seen in other countries (26), young age is itself an important risk factor for invasive NTS infection. Rates of infection in children under 5 years old are many-fold higher than in older children (10), and the highest rates of all are in the first year of life (27). However, infection is relatively uncommon in the first several months of life, peaking at around six months of age. This peak is a few months later than in developed countries, perhaps reflecting the waning of protection from maternal antibodies and from breastfeeding; as in other areas of the world, breastfeeding appears to be protective (22). It may also reflect rates of exposure to NTS from food, water, or environmental sources, though the sources of NTS infection in infants are not clearly known. Young age—less than a year old in a Kenyan study—is also a risk factor for greater disease severity (28).

Much research on invasive NTS infections in young children has focused on the role of malaria. Malaria—either concurrent or recent—is strongly associated at both the individual and population levels with invasive NTS infection (18, 27, 29, 30). Severe malaria is particularly strongly associated (25, 31). The reasons for this association are not fully understood but may involve effects on free iron availability (32), neutrophil function (33) and facilitation of NTS invasion of the bloodstream due to damage to the gut intestinal barrier (34, 35). The effect of malaria seems to be specific to NTS; whereas invasive NTS disease is strongly associated with malaria, other pathogens that cause bacteremia are not (10, 27, 36). Regardless of the reason, several studies conducted in various countries have shown marked reductions in invasive NTS infections with declining prevalence of malaria (16, 29, 37, 38). This gives hope that an effective malaria vaccine might indirectly lower risk of invasive NTS infection, at least to some extent.

Other well-documented risk factors for invasive NTS infection in children include malnutrition (18, 19, 23, 27), HIV infection (5, 18, 20, 30), anemia (27), concurrent schistosomiasis (39), and sickle cell disease. Although child malnutrition is common in the general population in much of sub-Saharan Africa, it is even more common in these children with invasive NTS infection. For example, in a multivariate analysis of data from Tanzania on children admitted to hospital with acute febrile illness, children with invasive NTS disease were twice as likely to have severe acute malnutrition as children with other diagnoses (27). In addition to its direct effects on the immune system, malnutrition can impair the intestinal endothelial barrier, which may predispose to invasion of NTS that might only have caused enteric infection otherwise. HIV infection is not as common in children as in adults with invasive NTS infection. Nonetheless, it is an important risk factor, especially in children who are not receiving antiretroviral therapy. Mortality in NTS infection exceeds 20% in children with HIV infection (19, 20, 30). In schistosomiasis, adult worms attach to the portal and mesenteric blood vessels. They are thought to provide a sanctuary for salmonellae to multiply and seed the bloodstream (39). Invasive NTS infection is also common in children with sickle cell anemia and other hemoglobinopathies. In coastal Kenya, about 5 to 10% of children hospitalized with invasive NTS disease had sickle cell disease (18). Few other studies of invasive NTS disease in Africa have documented sickle cell status, but it is known to be common throughout Africa and likely contributes to the overall burden of invasive NTS disease. Sickle cell disease, malaria, and malnutrition may all play a role in the observed association of invasive NTS disease with anemia. Not surprisingly, these risk factors appear to interact, with even higher risk of invasive NTS infection in children with two or more of the risk factors discussed above (16, 40).

Invasive NTS Infection in Adults

Early in the HIV epidemic, invasive NTS infection was recognized as a common presentation in severely immunocompromised patients (41). In Africa, the majority
of invasive NTS infection in adults occurs in patients with HIV infection (18, 42, 43), usually untreated. Like children, adults often present without a history of antecedent diarrhea, though diarrhea is more common in adults with invasive NTS disease than those who are admitted for other reasons (18). The presentation is commonly described as being consistent with enteric fever (44), although a septic picture is also common. Mortality is high, especially in patients with advanced HIV disease, in whom it can exceed 50% (42). However, even in HIV-negative patients, mortality of 32% was reported in Malawi (42). For survivors, recrudescent or recurrent invasive NTS infection occurs in a substantial proportion. HIV infection is a strong risk factor; recurrence has been reported to occur in more than 40% of HIV-infected patients with invasive NTS disease (43, 46).

**MICROBIOLOGY**

Although many *Salmonella* serotypes have been described, just a few are responsible for most invasive infections. In sub-Saharan Africa, the NTS serotypes that cause most invasive disease are Typhimurium and Enteritidis (8, 12, 14, 19, 24, 28, 42, 44, 47–50), which are also among the most common serotypes causing both gastrointestinal and invasive *Salmonella* infections globally. Although serotypes Typhimurium and Enteritidis appear to be frequent causes of invasive infection continent-wide, other serotypes have been reported in invasive infections, with specific serotypes appearing relatively frequently in specific geographic areas. Serotype Concord is a frequent cause of invasive infection in Ethiopia (51); serotype Isangi in South Africa (52); and serotypes Newport, Virchow, Derby, and Braenderup in Kenya (28, 53). Many other serotypes have been reported, though rarely.

Very limited information on the proportion of NTS infections that are invasive is available from Africa, in large part because microbiologic evaluation of diarrheal illnesses is quite rare, even in settings where blood and CSF cultures can be performed. Much of the information regarding the relative propensity of nontyphoidal serotypes to cause invasive disease comes from Kenya. This information reveals two patterns. First, a broader range of serotypes is isolated from stool than from blood. Second, however, the serotypes commonly isolated from blood are also commonly isolated from stool, though relatively less commonly than from blood. For example, in reports from the mid-1990s through the late 2000s from a hospital serving a rural population on the coast, *Salmonella* Typhimurium and Enteritidis accounted for 85 to 95% of *Salmonella* isolated from invasive infections in children but only 33 to 68% of *Salmonella* isolated from stool. By contrast, other serotypes accounted for up to 67% of *Salmonella* isolated from stool but less than 15% of invasive infections (24, 28, 54). Similarly, in a report from two other settings in Kenya covering 2006 through 2009, *Salmonella* Typhimurium accounted for 84% and 53% of *Salmonella* isolated from blood and stool, respectively (10). Given that the populations in which most invasive NTS disease occurs—young, often malnourished, children and HIV-infected adults—have compromised immunity, these data imply that *Salmonella* Typhimurium and Enteritidis are more prone than other serotypes to causing invasive disease in these immunocompromised populations. A similar observation was made early in the HIV epidemic in the United States, where surveillance data showed that *Salmonella* Typhimurium and Enteritidis, but not Heidelberg, were disproportionately associated with invasive infections in regions and age groups with a high prevalence of HIV infection (41).

*Salmonella* Typhimurium is particularly common in invasive infections in Africa, accounting for more than 90% of isolates in some series (44). In recent years, a specific strain of *Salmonella* Typhimurium, multilocus sequence type 313, or ST313, has caused epidemics of invasive disease (12). This strain was first recognized during the HIV epidemic that has been so prominent in Africa (55). Although ST313 does appear to be very prone to causing invasive infections in compromised hosts, apparently it also causes more typical gastrointestinal infections; a South African report notes that ST313 is commonly isolated from stool in diarrheal illness in otherwise healthy people (56). To the same point, six of nine ceftriaxone-resistant *Salmonella* Typhimurium isolates from people with severe illness in 2009 to 2011 characterized by whole-genome sequencing were from stool isolates. Although the multilocus sequence type was not reported, these isolates were genetically closely related and were likely ST313 (57).

In the last several years, many studies have used phenotypic and genetic methods to characterize ST313 strains. These strains initially fell into two (55, 58) and then three (59) distinct clusters based on genome sequencing comparisons. All three lineages are resistant to multiple antimicrobial agents, which likely contributed to their rapid clonal expansion in a population of susceptible NTS. Comparisons to other *Salmonella* Typhimurium strains indicated that eight ST19 strains that were associated with invasive disease in Africa were
scattered throughout the phylogenetic tree. This observation indicates that while other types may not be as common as ST313, they can also cause invasive disease in susceptible people in Africa. ST313 strains possess multiple pseudogenes, a characteristic which has been noted to be a marker for host adaptation. Different lineages possess somewhat different pseudogene repertoires. Roles for some of the pseudogenes in virulence for humans have been suggested. Phage type DT2 strains, which are known to be host-adapted to birds, were also noted to have multiple pseudogenes. In a whole-genome sequence comparison, ST313 strains appeared to be more closely related to the DT2 strains than to representative ST19 strains; a comparison of pseudogene profile between ST313 and DT2 was not made.

Experiments using in vitro models of infection to investigate potential virulence differences between ST313 and other S. Typhimurium strains have not provided a clear picture of the virulence properties of ST313. Using a mouse oral infection model, one study showed that an ST313 strain has a 50% lethal dose similar to an ST19 strain, while another showed similar levels of systemic colonization for ST313 and ST19 but a lower inflammatory response for ST313. A study using cell culture models showed that an ST313 strain produced less inflammatory response than an ST19 strain. In a chicken oral challenge model, both ST313 and ST19 strains caused invasive infections, with invasion occurring somewhat more slowly with the ST19 strain. A variety of macrophage models suggested that ST313 strains had a survival phenotype intermediate between ST19 strains, which were killed by human macrophages, and S. enterica serotypes Typhi and Paratyphi A, which are known to be highly invasive in humans and which survived and grew in human macrophages. The genetic diversity of Salmonella Typhimurium may be an explanation for the variable results in the in vitro models; results may depend on the model system used and the strains that are being compared.

Diversity in host range and ability to infect humans has been suggested for Salmonella Typhimurium. For example, phage type D2 has been noted to be adapted to birds and not commonly associated with human infections. Given the existence of Salmonella Typhimurium strains that are host-restricted to birds, it may be appropriate to consider the hypothesis that the apparent relative rarity of gastrointestinal infections due to ST313 in Africa is a reflection of low pathogenicity in healthy humans. Alternatively, it has been suggested that the spv genes found in some Salmonella serotypes including Salmonella Typhimurium and Enteritidis may contribute to more severe infections in immunocompromised individuals. Further understanding of the biological and epidemiological implications of the unique characteristics of ST313 could be valuable, particularly if it leads to a better understanding of sources of exposure, events leading to severe disease, and interventions that could decrease disease burden.

**SOURCES AND TRANSMISSION**

Known important routes of transmission for Salmonella worldwide include food-borne, waterborne, direct animal contact, and person-to-person routes. In the United States and other developed countries, food-borne transmission predominates. As summarized above, much is known about host risk factors for invasive NTS disease, such as HIV infection, malnutrition, malaria, and other host-compromising conditions. These host risk factors increase the risk of invasive disease occurring after exposure to NTS. They also confer greater risk for severe disease and death in those who become ill. Little is known, however, about risk factors for exposure to NTS in sub-Saharan Africa in the first place, and this lack of knowledge makes it difficult to design rational interventions to decrease exposure. By contrast, many studies have shown that risk factors for typhoid fever include crowding, poor sanitation, and lack of access to safe food and water. These factors relate to the risk of exposure to Salmonella Typhi itself and point directly toward interventions that can decrease the risk of disease. More information about the sources of exposure to NTS, especially Salmonella Typhimurium and Enteritidis, is urgently needed to inform disease control efforts.

Globally, much of what is known about routes of NTS transmission to humans comes from outbreak investigations that reveal sources and routes of exposure for a group of ill people with a source in common; reservoirs and sources vary by serotype. In sub-Saharan Africa, outbreak detection and investigation are less well developed, with no information on the sources of NTS outbreaks available from most countries. The few published outbreak investigations tend to be of outbreaks associated with institutions, especially hospitals. Since hospitalized populations are likely to include many people with host risk factors for invasive NTS disease, the occurrence of an outbreak associated with a hospital could be consistent with almost any route of transmission, especially food-borne, waterborne, and person-to-person. For instance, a primarily nosocomial outbreak of noninvasive Salmonella Typhimurium and Enteritidis may contribute to more severe infections in immunocompromised individuals. Further understanding of the biological and epidemiological implications of the unique characteristics of ST313 could be valuable, particularly if it leads to a better understanding of sources of exposure, events leading to severe disease, and interventions that could decrease disease burden.
Typhimurium infections was reported on a children’s ward in South Africa in 2012, but the investigation did not reveal a source or mode of transmission (73). By contrast, the investigation of a 2000–2001 nosocomial Salmonella Isangi outbreak from another South African hospital showed spread to patients in beds and cubicles contiguous to that of the index case, suggesting a role for either direct or indirect transmission from person to person (52).

Another approach to identifying sources of NTS has been to seek matching strains in household members, animals, and environments of patients. The most comprehensive of these studies, which was conducted in Nairobi slums, identified young children with invasive NTS disease and then did comprehensive culturing of family members, household and neighborhood animals, water sources, food, and local vendors. In all, NTS was isolated from 7% of family members, and the serotype matched in 65% of them (28). This observation does not elucidate whether the family members were simply exposed to the same source as the case or whether person-to-person transmission occurred. In this study, NTS was isolated from few nonhuman sources, but four isolates from water or soil matched the serotype and pulsed-field gel electrophoresis pattern of the isolate from the ill child (28). Again, though, detecting the same strain in the environment offers little insight into whether the patient was exposed through an environmental source, whether the patient contaminated the environment during the illness, or whether the NTS found in both the patient and the environment originated from another source, such as an animal.

Several studies have cultured livestock, poultry, and retail meats and have found NTS, often with a different distribution of serotypes than are found in humans (75–78). However, this pattern of differing serotype distributions is seen in settings where food-borne transmission is known to be common (79), so again it offers little clue as to sources. There are hints that poultry might be an important source of NTS in sub-Saharan Africa, as it is in the rest of the world. In Kenya, in the context of increasing incidence of human Enteritidis infections, a serotype strongly linked to eggs, investigators noted that rearing chickens for eggs had become increasingly common in the population (80). Finally, an intriguing study in South Africa compared pulsed-field gel electrophoresis patterns of NTS isolates from noninvasive human infections and captive wild animals, showing marked similarities in strains. This may imply a common source of exposure. The authors speculate that chicken, a common source of NTS globally, could be a source, since it is frequently part of the diet fed to captive wild animals (81).

In the absence of more definitive information on sources and routes of transmission, we are left to try to extrapolate from other information. The pronounced seasonality of invasive NTS disease, with increased incidence during and after the rainy season in Malawi (12), Kenya (28), and other countries has led some investigators to wonder whether this pattern implies an important role for waterborne transmission or whether general environmental contamination or person-to-person transmission might increase during the rainy season. Comparisons between NTS and Salmonella Typhi, which has a human reservoir, may offer other clues. In a 4-year study comparing the incidence of invasive NTS disease to typhoid fever in a rural and an urban setting in Kenya, NTS greatly predominated in the rural setting, whereas Typhi predominated in the urban setting (10). In Tanzania, a similar dichotomy was reported among children, with an NTS: Typhi ratio of 15:1 in the rural area and 1:6 in the urban area. It is tempting to speculate that this pattern might reflect sources of infection, with Typhi (human to human) being more common in the urban setting and NTS (animal to human) being more common in the rural setting. In summary, though, knowledge of the sources and routes of transmission of NTS in sub-Saharan Africa remains unclear at best, and this limits the ability to target interventions. In particular, if person-to-person transmission accounts for a large proportion of cases, then different interventions would be indicated than if, as in the rest of the world, contaminated food and water and contact with infected animals and environments are the major issues.

ANTIMICROBIAL RESISTANCE

Although antimicrobial therapy is not recommended for most uncomplicated gastrointestinal NTS infections, it is critically important for treatment of invasive infections. This was documented dramatically in an early paper on invasive NTS disease in Rwandan children, in whom mortality was 10% in those treated with an effective antibiotic (cefotaxime in this setting) but close to 80% in those who did not receive such treatment (22). Thus, the emergence and spread of resistance to antimicrobial agents commonly used for treatment of invasive NTS infections in Africa is an ominous development. This is especially true because the widespread limitations in microbiologic diagnostic capacity in much of Africa means that infections are often treated empirically. When resistance to empiric regimens emerges, it may not
be identified promptly, and large numbers of patients may not be treated with appropriate alternative agents, if alternatives are even available. Moreover, because children with invasive NTS infection may meet clinical criteria for pneumonia, which is usually caused by pathogens other than NTS, selection of antimicrobial agents poses a conundrum; agents that are recommended for empiric treatment of pneumonia, e.g., penicillin and chloramphenicol, are often ineffective in invasive NTS infection, and many agents effective against NTS are not ideal choices for the pathogens that cause pneumonia.

Beginning in the 1980s and accelerating since then, waves of antimicrobial resistance have greatly complicated the treatment of invasive NTS infections in Africa. The initial challenge was from resistance to several agents classically used for treatment of NTS infections, including chloramphenicol, ampicillin, and co-trimoxazole, as well as other agents. In Rwanda, invasive infections with such resistant isolates, as well as successful treatment with the third-generation cephalosporin, were described in children in the 1980s (17, 22). In Kenya in the mid-to-late 1990s, about half of invasive infections in children in a rural community were caused by NTS resistant to these agents (54), though resistance to chloramphenicol was somewhat less common. At that time, resistance to third-generation cephalosporins and fluoroquinolones was not seen (82). Similarly, in invasive NTS infections in adults in Kenya, the proportion resistant to these three agents was about 40% by 2003 (80). In Malawi in the late 1990s and early 2000s, successive epidemics of invasive infections resistant to these agents were caused by multi-drug resistant (MDR) Enteritidis and subsequently by MDR Typhimurium. In this primarily urban setting, resistance to all three agents increased rapidly over a period of several months to a year and a half from zero to about 80% of isolates (12). Whenever molecular characterization of resistance has been conducted, the resistance determinants have been shown to be plasmid-borne, implying that horizontal transfer between bacteria can readily occur. In sum, the emergence and spread of resistance to these inexpensive and widely available agents has essentially spelled the end of their usefulness for treatment of invasive NTS infections in many areas. Clinicians have had to turn to more expensive agents, such as third-generation cephalosporins (e.g., ceftriaxone) and fluoroquinolones (e.g., ciprofloxacin), when these agents were available.

Recently, NTS isolates with resistance to third-generation cephalosporins, and in some cases to fluoroquinolones as well, have become increasingly common. In 2000, a nosocomial outbreak of Isangi infections that produced an extended-spectrum beta lactamase (ESBL) and thus were resistant to ceftriaxone was reported from South Africa (52). Since then, Typhimurium resistant to third-generation cephalosporin has been reported from Malawi (83), Kenya (9, 57, 84), South Africa (3), and the Democratic Republic of the Congo (83). The Malawi report illustrates how quickly resistance can be acquired; the patient was a woman with HIV infection who had an initial NTS infection that was MDR but susceptible to ceftriaxone and ciprofloxacin. She was treated as an inpatient with ceftriaxone and discharged on oral ciprofloxacin and was readmitted a month later with recurrent disease; the isolate was MDR and also resistant to both ciprofloxacin and ceftriaxone (83). Genomic analysis suggested that this episode did not reflect reinfection with a new strain but rather acquisition of additional resistance determinants by the initial strain. Similarly, ceftriaxone resistance, along with resistance to multiple other agents, increased from less than 10% to more than 50% over about 2 years in NTS isolated in invasive Typhimurium infections in young children (9). An IncHI2 plasmid bearing CTX-M extended-spectrum beta-lactamase (ESBL) genes as well as genes conferring resistance to multiple other antimicrobial agents was identified in isolates from both Malawi and Kenya (57, 83), and beta lactamase genes of the TEM and CMY classes were reported from South Africa (3, 52). Fluoroquinolone resistance in isolates that do not produce ESBLs have also been reported (86). To our knowledge, NTS isolates resistant to carbapenems (e.g., imipenem, meropenem) have not been reported, but carbapenems are unavailable in most health care settings in Africa.

Antimicrobial resistance is complex, and although a pattern of increasing resistance has been seen in almost all studies, some exceptions exist. In a rural area of Kenya, a marked decrease in resistance to amoxicillin and co-trimoxazole in NTS isolated from children with invasive disease, from just under 70% to both agents in 1994–1997 to just over 10% in 2002–2005 was documented (53). While this offers hope that high rates of resistance might be reversible, information on antimicrobial usage trends in this area was not available, so it is not clear whether selective pressure was decreased or whether other factors, such as changes in medical care or in the distribution of NTS serotypes causing invasive disease, may have contributed to the decrease in resistance rates.

In summary, antimicrobial resistance poses a serious threat to our ability to treat invasive NTS infections in...
Afr. Effective antimicrobial stewardship—both for agents used in human medicine and for those used in animal agriculture—is critical to preserve the effectiveness of these agents. Antimicrobial agents are widely available without a prescription in most areas. Surveillance for antimicrobial resistance in NTS is needed to detect emerging resistance as early as possible. Protocols for empiric treatment need to reflect the prevailing resistance patterns while also acknowledging the limited availability and affordability of agents such as carbapenems and even third-generation cephalosporins (87)—a challenging task, indeed (87). That so many NTS isolates from invasive infections display resistance that makes them effectively untreatable, given the local availability of extended-spectrum agents, emphasizes the importance of primary prevention of invasive NTS infections.

INTERVENTIONS

Public health, environmental, and medical interventions to address the toll of invasive NTS disease in sub-Saharan Africa can be considered in three major categories—interventions to prevent exposure to NTS, interventions to prevent the occurrence of disease if exposure does occur, and interventions to prevent severe disease and death in those who become ill. All are important. Although, as discussed above, the routes of exposure to NTS in sub-Saharan Africa are not well understood, improvements in sanitation and hygiene in general are likely to decrease exposure to NTS by any route. Most enteric pathogens have transmission pathways in common, and it has been observed in other settings—for instance, when improvements in sanitation and hygiene undertaken in Mexico to control cholera were associated with marked decreases in all-cause diarrheal mortality in young children (88)—that such improvements have protean benefits. Nonetheless, better information about sources of NTS infection might help with the design of interventions that would be particularly appropriate for sub-Saharan Africa. Enhanced capacity for outbreak detection and investigation would be particularly valuable. Whole-genome sequencing also has promise as part of efforts to link human infections with their sources (56, 89).

Interventions to decrease the risk of progression to invasive infection after exposure to NTS are also critical. Several of the important risk factors for invasive NTS disease are themselves targets of concerted public health action. Great efforts have been and are being made to prevent HIV infection and to provide treatment when it occurs (90). Economic development as well as targeted programs can help to prevent childhood malnutrition. Malaria is also an enormously important public health problem (91), and efforts to control it through such measures as insecticide-treated bed nets appear to have had a major impact on invasive NTS disease as well as on malaria itself. The possibility that an effective malaria vaccine would have indirect impact in preventing invasive NTS disease is exciting and important. A recent study from Malawi modeling the impact of HIV infection, acute malnutrition, malaria, and other factors on invasive NTS disease validated the notion that public health interventions to reduce them have likely had both individual and synergistic impact on rates of invasive NTS disease in children (16).

Effective NTS vaccines are an attractive idea. Studies in Malawi have demonstrated that most children developed anti-NTS antibodies by two years of age, as well as cell-mediated immunity, and that this antibody enabled NTS killing in vitro, suggesting that a vaccine that stimulates production of such antibodies might be possible (92, 93). Several candidate live attenuated vaccines and glycoconjugate vaccines targeted at serogroup-specific surface antigens have been developed and are in early development (14, 94–99). Although these vaccines are promising, it is difficult to predict whether any of them would be safe and effective. It is unlikely that an NTS vaccine could be licensed and available in less than 5 to 10 years, so other actions to control invasive NTS disease should not be postponed in anticipation of a vaccine.

Finally, prevention of severe infection and death will rely not only on general development of the medical system, including primary prevention through infection prevention and control within health care facilities, but also on the availability of effective antimicrobial agents to treat these infections. The emergence and spread of antimicrobial resistance has rightly been described as a public health crisis that threatens the ability to treat many infections, invasive NTS disease among them (100). Global, regional, and local action to preserve the effectiveness of antimicrobial agents involves surveillance for the emergence and prevalence of resistance and stewardship of antimicrobial agents used for humans and for animals. Already, many invasive NTS infections are essentially untreatable in many health care facilities in sub-Saharan Africa, and prevention of further development and spread of resistance is urgently needed.
CONCLUSION

Invasive nontyphoidal *Salmonella* (NTS) infections in Africa cause an enormous burden of illness and high mortality and, in some areas, NTS is the most common cause of invasive bacterial infection. Populations with compromised immunity—young children, especially those with malnutrition or malaria, and HIV-infected adults—are at the highest risk. As in the rest of the world, Typhimurium and Enteritidis are the most common serotypes causing invasive NTS infections in Africa. A specific strain of Typhimurium, multilocus sequence type 313, has recently caused epidemics of invasive disease. Antimicrobial therapy is critically important for treatment of invasive NTS infections. Waves of antimicrobial resistance, recently including third-generation cephalosporins, have emerged and spread across the continent, threatening the ability to treat these infections. Improvements in antimicrobial stewardship are important in Africa, as in the rest of the world. Several NTS vaccines are in early development and, if shown to be safe and effective, could be promising, but vaccines will not be widely available for years, so other control strategies must also be pursued. Because of the strong association of invasive NTS disease in children with malaria, effective malaria control programs may also help reduce invasive NTS disease to some extent. Little is known about the sources of exposure to NTS in Africa or about the relative importance of foodborne or waterborne transmission or direct contact with infected animals or people, making the rational design of interventions to prevent exposure difficult. However, improved sanitation and access to safe water and food would likely have an important impact on exposure to NTS in Africa.

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REFERENCES


Mahon and Fields

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