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Clinical and Microbiological Features of *Salmonella* Meningitis in a South African Population, 2003–2013

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Abstract

Background—The clinical and microbiological characteristics of nontyphoidal *Salmonella* (NTS) meningitis in South Africa, where human immunodeficiency virus (HIV) prevalence is high (approximately 15% in persons ≥15 years of age), were reviewed.

Methods—From 2003 through 2013, 278 cases were identified through national laboratory-based surveillance. Clinical information (age, sex, outcome, Glasgow Coma Scale [GCS], and HIV status) was ascertained at selected sites. Isolates were serotyped; susceptibility testing and multilocus sequence typing on *Salmonella enterica* serovar Typhimurium isolates was performed. Multivariable logistic regression was used to determine factors associated with mortality outcome, using Stata software, version 13.

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Results—Where age was ascertained, 139 of 256 (54.3%) patients were <15 years. Males represented 151 of 267 (56.6%). Mortality outcome was recorded for 112 of 146 (76.7%) enhanced surveillance patients; 53 of 112 (47.3%) died. Death was associated with GCS ≤13 (adjusted odds ratio [OR], 18.7; 95% confidence interval [CI], 3.0–118.5; *P* = .002) on multivariable analysis. Where data were available, all 45 patients aged >15 years were HIV infected, compared with 24 of 46 (52.2%) patients aged <5 years. Neonates were less likely to be HIV infected than infants aged 2–12 months (OR, 4.8; 95% CI, 1.1–21.1; *P* = .039).

Salmonella—Typhimurium represented 106 of 238 (44.5%) serotyped isolates: 65 of 95 (68.4%) were ST313 vs ST19, respectively, and significantly associated with HIV-infected patients (*P* = .03) and multidrug resistance (OR, 6.6; 95% CI, 2.5–17.2; *P* < .001).

Conclusions—NTS meningitis in South Africa is highly associated with HIV in adults, with neonates (irrespective of HIV status), and with *Salmonella* Typhimurium ST313. GCS is the best predictor of mortality: early diagnosis and treatment are critical. Focused prevention requires further studies to understand the sources and transmission routes.

Keywords

Salmonella; meningitis; HIV; *Salmonella* Typhimurium ST313

Bacterial meningitis in Africa remains an important disease with a high associated mortality [1–7]. Meningitis in human immunodeficiency virus (HIV)–infected persons is frequently associated with cryptococcosis, tuberculosis, and *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis* [3, 4, 8–12]. Numerous other pathogens have been described as a cause of meningitis among HIV-infected persons [1, 7, 9, 12, 13]. Nontyphoidal *Salmonella* (NTS) is emerging as a significant meningeal pathogen among HIV-infected persons, following the decline in incidence of *S. pneumoniae* and Hib with the introduction of pneumococcal conjugate and Hib conjugate vaccines [1, 6, 9, 12–14]. In previous series, in adults from South African institutions, NTS meningitis represented 16% of acute bacterial meningitis cases among HIV-infected patients [7]. An estimated 8% of all meningitis cases for which a microbiological diagnosis was made was attributed to acute bacterial meningitis [15]. NTS meningitis was not reported in pediatric series [16, 17].

The association between HIV and invasive NTS infections, including meningitis, was described early in the AIDS epidemic [18]. Case reports of adults with NTS meningitis frequently describe an association with HIV [7, 18–20], although other immunosuppressive conditions have been described [21–23]. Molyneux et al described NTS meningitis in a cohort of 105 Malawian children, aged between 2 months and 16 years, over a 10-year period [2]. Approximately half were HIV infected, and 12.4% were infected with malaria; mortality rates were >50% [2]. There are rare reports of NTS meningitis in previously healthy individuals [24], suggesting that comorbidity is common, but not an absolute prerequisite to infection.

A meta-analysis of published African studies suggests that *Salmonella* bacteremia accounts for 21.4% of all bacteremias [25], with an incidence rate of 227 per 100 000 [26]. In contrast, *Salmonella* meningitis accounted for <10% of all-cause meningitis (incidence rate

of 20/100 000) in Malawian patients in 2012 [6], suggesting approximately 1% of NTS bacteremias results in meningitis. *Salmonella enterica* serovars Typhimurium and Enteritidis account for 65.2% and 33.1% of all invasive NTS infections, respectively [25], and similar observations have been made regarding the frequency with which these serovars occur in NTS meningitis [2]. In the past 30 years, the emergence of invasive *Salmonella* Typhimurium ST313, a sequence type associated with the African AIDS epidemic, has been highlighted [27, 28].

We describe the clinical and microbiological data associated with a series of patients presenting with NTS meningitis in South Africa, a country that is largely malaria-free, with high HIV prevalence affecting approximately 15% of the population ≥15 years of age [29], to better understand the association with HIV, potential predisposing conditions, and the role of *Salmonella* Typhimurium ST313.

METHODS

Case Definition

National active laboratory-based surveillance for invasive salmonellosis, defined as the isolation of NTS from a normally sterile body site, including *Salmonella* meningitis, was performed by the Centre for Enteric Diseases (CED) of the National Institute for Communicable Diseases in South Africa from 2003 through 2013, as previously described [30]. A case of NTS meningitis was defined as any patient from whom NTS was isolated from cerebrospinal fluid (CSF). A nosocomial infection was defined as NTS meningitis infection in a patient in whom the diagnosis of meningitis was made ≥48 hours after the patient had been admitted to a medical or long-term-care facility. We used the annualized South African population from 2003 to 2013, which increased from 45.80 million to 52.98 million over the period, to calculate incidence (http://www.statssa.gov.za/publications).

All diagnostic microbiology laboratories in South Africa were requested to submit *Salmonella* isolates from patients fulfilling the case definition, for serotyping and susceptibility testing, supplemented by audits from 2005 to identify isolates not received by the reference laboratory. Additional clinical information was collected on cases at 24 sentinel hospitals in 9 provinces through the Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa network, a national surveillance system sharing resources to monitor diseases of public health importance. This included data on HIV status, other immunosuppressive conditions, admission and discharge dates, antibiotic exposure, timing of meningitis diagnosis (number of hours after patient admission), and disease outcome.

Laboratory Characterization

All *Salmonella* isolates received were serotyped by CED according to established protocols (Mast Group, Merseyside, United Kingdom; Bio-Rad, Marnes-la-Coquette, France; Remel, Kent, United Kingdom; Statens Serum Institut, Copenhagen, Denmark). Minimum inhibitory concentrations (MICs) were determined for the following antimicrobials: ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole (cotrimoxazole), tetracycline,

ciprofloxacin, ceftriaxone, and ceftazidime, using Etest strips according to the manufacturer's instructions (bioMérieux, Marcy-l'Étoile, France). Multidrug resistance was defined as resistance to ≥3 of these antimicrobials. Production of extended-spectrum β-lactamase was tested for using the Mast Laboratories double disk method, according to the manufacturer's instructions (Mast Diagnostics, Bootie, England).

Genotypic Characterization of *Salmonella* Typhimurium

Genotyping of *Salmonella* Typhimurium isolates was performed using multilocus sequence typing (MLST), as described at the *Salmonella* MLST database (http://mlst.warwick.ac.uk/mlst/dbs/Senterica), including DNA sequencing analysis of the following 7 housekeeping genes: *aroC*, *dnaN*, *hemD*, *hisD*, *purE*, *sucA*, and *thrA*. DNA sequencing was performed using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, California) and an Applied Biosystems 3500 Genetic Analyzer. DNA sequences were collated and analyzed using the DNASTAR Lasergene (version 8.0) software (DNASTAR, Inc, Madison, Wisconsin), followed by analysis at the *Salmonella* MLST database, where allele numbers and a MLST sequence type (ST) were assigned.

Ethical Approval

Ethical approval for this study was granted by the Human Research Ethics Committee of the University of the Witwatersrand (M110601).

Statistical Analysis

Variables analyzed included age, sex, HIV status, Glasgow Coma Scale (GCS), nosocomial infection, cotrimoxazole prophylaxis, use of antiretrovirals (ARVs), $CD4^+$ count, other comorbid conditions, isolation of *Salmonella* Typhimurium or multidrug-resistant *Salmonella*, and *Salmonella* sequence type. Clinically relevant groupings were created for continuous variables, to aid interpretation of results. Univariate and multivariate logistic regression were used to determine factors associated with mortality. Multivariate analysis using a manual forward stepwise progression was used, with a cutoff of $P < .1$ for the univariate analysis, dropping nonsignificant factors. Model fit was assessed by using the Hosmer–Lemeshow goodness-of-fit test. Analysis was performed using Stata version 13 (StataCorp, College Station, Texas). Two-sided P values of <.05 were considered significant throughout. Due to the nature of the study, important variables had missing data. For both univariate and multivariate analyses, a complete case analysis was conducted in which patients with missing data were excluded from the analysis.

RESULTS

Cumulative Data

Figure 1 summarizes case numbers, including relevant clinical and microbiological data pertaining to these. We identified a total of 278 cases of laboratory-confirmed NTS meningitis in South African hospitals from 2003 through 2013, representing 3.3% of all invasive salmonellosis (Figure 1). Bimodal peaks of disease incidence were observed in children <5 years of age and adults >15 years of age (Figure 2*A*). NTS was isolated from the CSF only in 196 (70.5%) patients; NTS was additionally isolated from blood, stool, or other

body sites of 82 (29.5%) patients. The average incidence of NTS meningitis during the period was 5 per 10 000 000 per year. Clinical data are summarized in Table 1.

Clinical Data

Additional clinical information was available from 146 (52.5%) patients with NTS meningitis: 112 had a known outcome (76.7%) (Figure 1), and 111 (99.1%) and 82 (73.2%) had an available age and HIV status, respectively. Sex was recorded in 267 patients: 151 of 267 (56.6%) were male. Table 2 summarizes clinical risk factors for mortality. Nineteen of 58 (32.8%) children aged <15 years died, compared with 34 of 53 (64.2%) patients aged ≥15 years (P = .001; Table 2, Figure 2*B*). HIV status was recorded for 92 of 146 (63.0%) patients; 70 (76.1%) were HIV infected (Figure 2*C*). Among patients with recorded age and HIV status, all 45 patients aged ≥15 years were HIV infected, compared with 24 of 46 (52.2%) patients aged <5 years (Figure 2*C*). Children aged between 5 and 15 years had no outcome or HIV data recorded. Nine of 11 (81.9%) infants aged >1 year for whom data were available had a history of HIV exposure at birth.

Neonates were significantly less likely to be HIV infected than infants aged between 2 months and 1 year (3/12 [25.0%] vs 19/31 [61.3%]; odds ratio [OR], 4.8; 95% confidence interval [CI], 1.1–21.1; P = .039); however, there was no difference in mortality between the 2 groups (7/18 [38.9%] vs 12/38 [31.6%]; OR, 0.7; 95% CI, .2–2.3; P = .590). Nosocomial NTS meningitis was diagnosed in 13 of 118 (11.0%) patients for whom admission dates were available.

The length of hospital stay varied between 0 and 77 days (median of 12 days). Cases were 7 times more likely to die within the initial 10 days of their hospital stay (OR, 7.1; 95% CI, 3.1–16.4; P < .001). There was no significant association between nosocomial vs community-acquired infections and mortality (Table 2).

$CD4^+$ cell counts were available for 33 of 146 (22.6%) patients. A $CD4^+$ count <200 cells/μL was not significantly associated with mortality (Table 2). Whether the HIV-infected patients received ARVs was recorded for 41 patients with NTS meningitis; 10 (24.4%) received ARVs at the time of diagnosis of NTS meningitis. There was no significant effect on the mortality between HIV-infected persons on ARVs and those not on ARVs (P = .7; Table 2).

The GCS was recorded for 43 patients: 7 of 43 (16.3%) had a GCS ≤13. For the 35 (81.4%) patients with GCS recorded for whom HIV status was known, 9 of 10 HIV-uninfected patients had a GCS >13 (90.0%), compared with 18 of 25 (72.0%) HIV-infected patients. Multivariable analysis confirmed that mortality was associated with a GCS ≤13 (adjusted OR, 18.7; 95% CI, 3.0–118.5; P = .002; Table 2). The Hosmer–Lemeshow goodness-of-fit test confirmed the fitness of the model (χ^2 = 0.04, P = .8411).

Comorbidities potentially associated with NTS meningitis were recorded in 45 of 124 (36.2%) patients. Laboratory-confirmed cryptococcal meningitis was diagnosed in 3 of 45 (6.7%); 5 of 45 (11.1%) had a history of head injury; and 29 of 45 (64.4%) were receiving therapy for tuberculosis or had a history of active tuberculosis, but the site of tuberculosis

infection was not stated (ie, pulmonary vs extrapulmonary or central nervous system infection). One HIV-uninfected 3-month-old infant receiving treatment for tuberculosis had a GCS of 1. No patients were coinfected with other etiological agents of acute bacterial meningitis (*S. pneumoniae*, *N. meningitidis*, or Hib). None of the patients had malaria.

In addition, 81 of 146 (55.5%) patients had data on cotrimoxazole prophylaxis. Cotrimoxazole prophylaxis was not significantly associated with outcome ($P = .3$; Table 2). Individual patient records suggested that all patients received appropriate antimicrobial therapy for NTS meningitis on admission or were changed to appropriate antimicrobial therapy once susceptibility data were available for the *Salmonella* isolated from the patients' CSF.

Microbiological Data

Microbiological characterization was undertaken on 247 of 278 (88.8%) isolates. *Salmonella* Typhimurium predominated (Table 3).

Patient outcome information was available for 111 of 247 (44.9%) cases with NTS serovar and antimicrobial susceptibility data. Patients infected with *Salmonella* Typhimurium were more likely to die compared with other serovars on univariate analysis ($P = .006$); this was not significant on multivariable analysis (Table 2). Death rates were not significantly higher in those patients who had multidrug-resistant isolates.

Where HIV status was known, 39 of 70 (55.7%) HIV-infected patients had meningitis due to *Salmonella* Typhimurium, compared with 31 of 70 (44.3%) HIV-infected patients with NTS meningitis due to other serovars, although this was not significant ($P = .08$).

Multidrug resistance (defined above) was detected in 103 of 247 (41.7%) of the isolates; 56 of 247 (22.7%) were resistant or intermediately resistant to ciprofloxacin (Table 3). *Salmonella enterica* serovar Isangi and serovar Virchow isolates were more likely to be extended-spectrum β-lactamase producers than other serovars (20/30 [66.7%] for *Salmonella* Isangi and *Salmonella* Virchow vs 17/247 [6.9%] for other serovars; OR, 46.1; 95% CI, 15.4–138.3). *Salmonella* Typhimurium was more likely to be multidrug resistant than other serovars (62/104 [59.6%] vs 34/143 [23.8%] for other serovars; OR, 4.7; 95% CI, 2.7–8.2; $P < .001$).

MLST of *Salmonella* Typhimurium

Ninety-seven of 104 *Salmonella* Typhimurium isolates (93.3%) were MLST subtyped (Table 4). There was a trend toward association of outcome with meningitis due to *Salmonella* Typhimurium ST313 on univariate analysis ($P = .056$; Table 2). HIV-infected patients were significantly more likely to be infected by *Salmonella* Typhimurium ST313 ($P = .03$) compared with other sequence types (Table 4). *Salmonella* Typhimurium ST16 and ST302 were isolated from HIV-uninfected patients.

Multidrug resistance was significantly associated with *Salmonella* Typhimurium ST313 (48/65 [73.8%]) compared with *Salmonella* Typhimurium ST19 (9/30 [30.0%]) (OR, 6.6; 95% CI, 2.5–17.2; $P < .001$).

DISCUSSION

To our knowledge, this is the largest series of *Salmonella* meningitis described. Molyneux et al [2] described a large series in children aged 2 months to 16 years in Malawi. Predisposing conditions in Malawi included HIV infection and malaria [2]. An earlier publication has highlighted NTS as a cause of meningitis in HIV-infected South African adult patients and described the associated characteristics [7], NTS meningitis representing approximately 1.3% of all-cause meningitis in this age group [15]. Previously, we have compared South African and Malawian data, reviewing the role of NTS in invasive disease in these 2 countries. The countries both showed a bimodal age distribution, with disease occurring primarily in young children and adults aged 20–50 years, confirming the importance of these ages in association with invasive disease due to NTS [31].

Our report again highlights the vulnerability of children aged <5 years to NTS meningitis. All the adults in our series and 58% of children <5 years of age were HIV infected, although none had malaria. A similar distribution in patients' ages occurs with invasive shigellosis in South Africa, with excessive case numbers occurring in the very young and a second peak from early adulthood [30].

In addition to our series, the strong association of NTS meningitis with HIV infection in adults is suggested by case reports in the literature [18–20, 32]. Predisposing conditions, which we did not observe, include autoimmune conditions or other coinfections [21–23]; rarely, patients may have no predisposing conditions [24].

In the follow-up of the Malawian pediatric meningitis cases, impaired consciousness was significant in the outcome of cases of NTS meningitis [1]. We had similar findings in adults and children. Patients presenting with a GCS ≤13 were at a greater risk of death, irrespective of HIV status. Of note, none of the HIV-uninfected patients who had a recorded GCS >13 died. Previous reports from South Africa on meningitis due to *N. meningitidis* and *S. pneumoniae* emphasize the significance of severity of illness at presentation [3, 4].

Death rates in children in our series were lower than those described in the Malawian series [1, 2]; almost half of the deaths were in adults. Wall et al reviewed meningitis due to all causes in adolescents and adults in Malawi and similarly found that GCS was the strongest independent predictor of mortality, using a cutoff of 11 rather than 13 [5].

Irrespective of age, HIV infection was a major contributing factor for death in the univariate model. In South Africa, excessive deaths due to meningococcal and pneumococcal meningitis in association with HIV infection have been reported [3, 4], emphasizing the vulnerability of these patients to severe infections. In Malawian adults, mortality due to bacterial meningitis increased over time [5, 6]: we did not follow patients after discharge, but longer hospital stay was associated with improved survival in our series.

Antiretroviral therapy did not impact mortality in this study, stressing the importance of early diagnosis and treatment of NTS meningitis. Our patients also received appropriate antimicrobial therapy; incorrect treatment did not play a major role in the outcome. We

postulated that other comorbidities may have contributed to the development of NTS meningitis, but data were too scanty to develop definitive conclusions.

Neonates and young children are particularly vulnerable groups warranting further consideration. We did not have access to information posthospitalization, but the Malawian study suggested that infants and young children who recover from the acute infection are susceptible to neurological sequelae [1, 2]. Although mortality was independent of HIV status in our series, a greater proportion of infants who acquired NTS meningitis were HIV exposed at birth. Absence of maternal immunity in HIV-infected mothers may increase the risk in infants to acquiring NTS meningitis, which should be included in the differential diagnosis of causes of neonatal and infant meningitis in settings of high HIV seroprevalence [13, 33–36]. Previously, we described the role of childhood *Shigella* infections predisposing HIV-infected women to invasive shigellosis [30]. In this instance, the reverse appears to be true: Maternal HIV infection may predispose neonates to invasive salmonellosis, confirming the importance of maternal health and a competent immune system in decreasing infant mortality in South Africa [37].

In immunosuppressed patients, whether due to HIV infection or extreme youth, innate characteristics of *Salmonella* may predispose the organism to invading the central nervous system. *Salmonella* Typhimurium has the ability to adhere to, penetrate, and invade the brain microvascular endothelium, in association with a proinflammatory immune response [38]. Our understanding of the organism may need to be altered to adapt to new management paradigms; following the introduction of new vaccines to prevent childhood meningitis, new pathogens associated with meningitis may be seen to emerge [9, 12, 13].

Salmonella serovar was a better predictor of outcome than multidrug resistance: *Salmonella* Typhimurium was more highly associated with death. *Salmonella* Typhimurium ST313 is well associated with HIV [27]; we found that the organism contributes significantly to NTS meningitis in HIV-infected patients. Besides ST313, representing 67% of typed *Salmonella* Typhimurium isolates, ST19 represented 31% of typed isolates; ST19 is commonly described worldwide, including from South Africa [39]. A stronger association between HIV infection and *Salmonella* meningitis due to *Salmonella* Typhimurium ST313, compared with *Salmonella* Typhimurium ST19, was noted. In our previous report of predominantly noninvasive *Salmonella* Typhimurium ST19 infection, most of the patients were HIV uninfected [39].

To prevent NTS meningitis infections, further studies are needed regarding the source of infections in South Africa. We demonstrated that nosocomial NTS meningitis was rare; infections were likely community acquired. *Salmonella* are ubiquitous, and the association between foodborne disease transmission and human-to-human transmission with invasive disease is recognized [24, 40, 41]; although transmission is often assumed to be foodborne, actual routes are not always clear. Attention should be paid to preventing mother-to-child transmission, including maternal screening for fecal pathogens, and ensuring maternal health in a potentially disadvantaged subset of HIV-infected individuals [37, 42–45].

This study had limitations. Clinical data were collected at selected sites only and may not be relevant to all the cases, and clinical data were often incomplete. Not all patients at enhanced sites had outcome data, HIV results, $CD4^+$ counts, and access to ARV treatment. Data on tuberculous meningitis, prior treatment for cryptococcal meningitis, or acute bacterial meningitis were not collected. Insufficient data were collected on maternal HIV status in pediatric cases, and this impact could not be fully assessed. Fecal cultures were not performed on the mothers of infants in association with meningitis; we cannot comment on whether maternal carriage of NTS contributed to infection in infants. Incomplete clinical data meant that the ubiquity and consequences of *Salmonella* Typhimurium ST313 in NTS meningitis could not be fully elucidated. We elected not to do imputations for the missing data, believing that on univariate analysis at least, sufficient association was shown between outcome, age, HIV status, GCS, *Salmonella* Typhimurium, and *Salmonella* Typhimurium sequence types to highlight critical factors associated with *Salmonella* meningitis. Considering the high proportion of missing data in our data set, imputation (especially of binary data) could lead to biased inference. The complete case analysis that was conducted in this study assumes that data are missing completely at random. Our data may not be missing completely at random—but rather missing at random where relevant information regarding outcome, HIV result, or consent at a sentinel site was not collected—or not missing at random: Sentinel hospitals are typically referral hospitals where HIV-infected persons may preferentially present. We do believe we identified the majority of NTS meningitis cases over the period; typically in South Africa, patients with suspected meningitis will have lumbar punctures performed and CSF samples submitted to the laboratory for culture.

In conclusion, we describe a national series of laboratory-confirmed meningitis cases due to NTS over an 11-year period, highlighting the importance of disease severity as measured by GCS, HIV status in adults, and infection in neonates and infants, and the association of outcome and HIV status with specific serovars and sequence types. Early diagnosis and appropriate therapy may decrease death rates, and optimizing maternal health may lower case numbers in neonates and infants. Better understanding of the role of *Salmonella* Typhimurium, specifically *Salmonella* Typhimurium ST313, may also assist in controlling invasive disease due to NTS.

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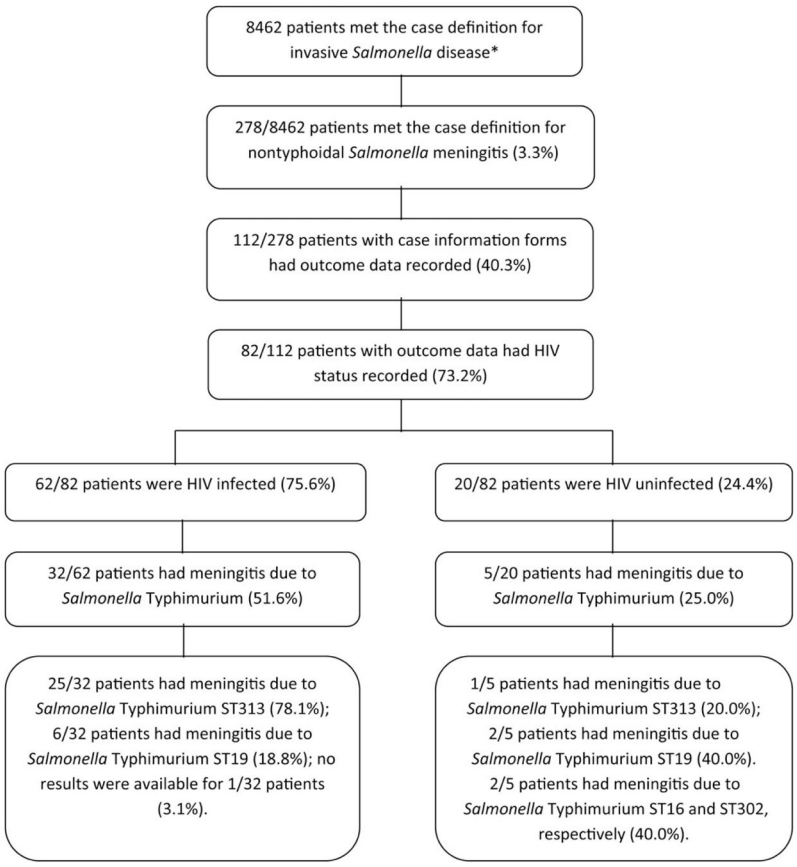

Figure 1.

Patients with nontyphoidal *Salmonella* (NTS) meningitis identified in South Africa, 2003–2013. *Invasive disease was defined as the isolation of NTS from a normally sterile body site. Abbreviations: HIV, human immunodeficiency virus; ST, sequence type.

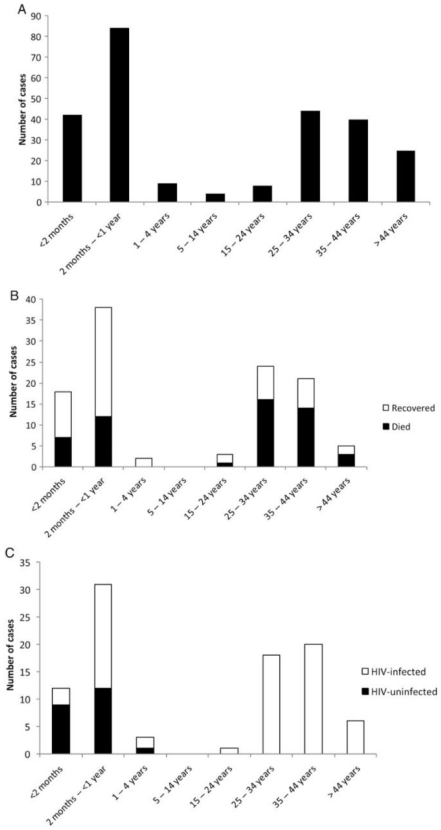

Figure 2.

A, Number of cases of nontyphoidal *Salmonella* (NTS) meningitis (n = 256) by age group, 2003–2013. *B*, Number of cases of NTS meningitis (n = 111) by age group and mortality, 2003–2013. One patient who recovered did not have an age recorded. *C*, Number of cases of NTS meningitis (n = 91) by age group and human immunodeficiency virus (HIV) status, 2003–2013. One HIV-infected patient did not have an age recorded.

Table 1

Clinical Characteristics Associated With Patients With *Salmonella* Meningitis in South Africa, 2003–2013

Characteristic	Outcome		Total,[a] No. (%)	*P* Value
	Survived, No. (%)	Died, No. (%)		
Data from all cases			278 (100)	
Age				
<2 mo	11 (26.2)	7 (16.7)	42 (16.4)	…
2 mo to <1 y	26 (30.9)	12 (14.3)	84 (32.8)	.5
1–4 y	2 (22.2)	0 (0.0)	9 (3.5)	.2
5–14 y	…	…	4 (1.6)	…
15–24 y	2 (25.0)	1 (12.5)	8 (3.1)	.9
25–34 y	8 (18.2)	16 (36.4)	44 (17.2)	.07
35–44 y	7 (17.5)	14 (35.0)	40 (15.6)	.08
>44 y	2 (8.0)	3 (12.0)	25 (9.8)	.4
Sex				
Female	20 (17.2)	26 (22.4)	116 (43.4)	…
Male	37 (24.5)	26 (17.2)	151 (56.6)	.1
Sentinel site data	59 (52.7)	53 (47.3)	112 (52.5)	
HIV status				
Uninfected	17 (77.3)	3 (13.6)	22 (23.9)	…
Infected	32 (45.7)	30 (42.9)	70 (76.1)	.008
Glasgow Coma Scale				
≤13	2 (20.0)	8 (80.0)	10 (23.3)	…
>13	27 (81.8)	5 (15.2)	33 (76.7)	.3
Nosocomial infection				
No	52 (51.5)	45 (44.6)	101 (88.6)	…
Yes	6 (46.2)	6 (46.2)	13 (11.4)	.8
Cotrimoxazole prophylaxis				
No	40 (65.6)	20 (32.8)	61 (75.3)	…
Yes	10 (50.0)	9 (45.0)	20 (24.7)	.3
Antiretrovirals				
No	31 (57.4)	22 (40.7)	54 (78.3)	…
Yes	9 (60.0)	5 (33.3)	15 (21.7)	.7
CD4 count, cells/μL				
≤200	10 (34.5)	16 (55.2)	29 (87.9)	…
>200	2 (50.0)	2 (50.0)	4 (12.1)	.7
Other comorbidity				
No	40 (50.6)	29 (25.3)	79 (63.7)	…
Yes	19 (42.2)	24 (53.3)	45 (36.3)	.2
Salmonella serotype				

Characteristic	Outcome		Total,[a] No. (%)	*P* Value
	Survived, No. (%)	Died, No. (%)		
Enteritidis	21 (55.3)	12 (31.6)	38 (26.0)	…
Typhimurium	17 (27.4)	29 (46.8)	62 (42.5)	.02
Other	21 (45.7)	12 (26.1)	46 (31.5)	.2
Salmonella multidrug resistance				
No	40 (46.5)	27 (31.4)	86 (63.7)	…
Yes	16 (32.7)	22 (44.9)	49 (36.3)	.08
Salmonella Typhimurium sequence type				
ST19	6 (35.3)	4 (23.5)	17 (30.9)	…
ST313	8 (21.1)	23 (60.5)	38 (69.1)	.05

Abbreviations: HIV, human immunodeficiency virus; ST, sequence type.

[a]Total includes those patients for whom outcome was unknown.

Table 2

Univariate and Multivariate Analysis of Risk Factors Associated With Mortality in Patients With *Salmonella* Meningitis in South Africa, 2003–2013

	Univariate Analysis			Multivariate Analysis		
Characteristic	**OR**	**(95% CI)**	***P* Value**	**AOR**	**(95% CI)**	***P* Value**
Age						
<15 y	1	…	…	1	…	…
≥15 y	3.7	(1.7–8.1)	.001	2.3	(.4–12.1)	.338
Sex						
Male	1	…	…			
Female	1.9	(.9–4.0)	.117			
HIV status						
Uninfected	1	…	…	1	…	…
Infected	5.3	(1.4–20.0)	.013	0.9	(.1–15.7)	.987
Glasgow Coma Scale						
≤13	1	…	…	1	…	…
>13	21.6	(3.5–133.3)	.001	18.7	(3.0–118.5)	.002
Nosocomial infection						
No	1	…	…			
Yes	1.1	(.3–3.7)	.844			
Cotrimoxazole prophylaxis						
No	1	…	…			
Yes	1.8	(.6–5.1)	.272			

	Univariate Analysis			Multivariate Analysis		
Characteristic	**OR**	**(95% CI)**	***P* Value**	**AOR**	**(95% CI)**	***P* Value**
Antiretrovirals						
No	1	…	…			
Yes	0.8	(.2–2.7)	.695			
$CD4^+$ count, cells/μL						
≤200	1	…	…			
>200	0.6	(.8–5.2)	.663			
Other comorbid conditions						
No	1	…	…			
Yes	1.7	(.8–4.0)	.157			
Salmonella serotype						
Other serotypes	1	…	…	1	…	…
Typhimurium	3.0	(1.3–6.5)	.006	0.6	(.1–4.8)	.659
Salmonella multidrug resistance						
No	1	…	…	1	…	…
Yes	2.0	(.9–4.6)	.084	0.6	(.1–5.5)	.648
Salmonella Typhimurium sequence type						
ST313	1	…	…	1	…	…
ST19	0.2	(.05–1.04)	.056	1.0	(.04–23.0)	.994

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; ST, sequence type.

Table 3

Commonest *Salmonella* Serotypes, 2003–2013, and Antimicrobial Resistance Profiles (n = 247) Associated With *Salmonella* Meningitis in South Africa

	Selected Antimicrobials Tested Against Strains of Nontyphoidal *Salmonella*					
Serotype (No. Tested)	**Ampicillin[a]**	**Chloramphenicol[a]**	**TMP-SMX[a]**	**Tetracycline[a]**	**Ciprofloxacin[a]**	**ESBL Production[a,b]**
Typhimurium (104)	72 (69.2)	39 (37.5)	67 (64.4)	47 (45.1)	30 (28.8)	9 (8.6)
Enteritidis (66)	5 (7.6)	3 (435)	3 (4.5)	8 (12.1)	14 (21.2)	1 (1.5)
Isangi (15)	14 (93.3)	13 (86.7)	14 (93.3)	15 (100.0)	9 (60.0)	12 (80.0)
Virchow (10)	9 (90.0)	7 (70.0)	8 (80.0)	8 (80.0)	0 (0.0)	8 (80.0)
Dublin (10)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other (42)	10 (23.8)	9 (21.4)	12 (28.6)	17 (40.5)	3 (7.1)	6 (14.3)

Data are presented as No. (%). Complete antimicrobial resistance data were not available for all serotypes tested.

Abbreviations: ESBL, extended-spectrum β-lactamase; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] No. of intermediate and fully resistant isolates.

[b] Production of extended-spectrum β-lactamase.

Clin Infect Dis. Author manuscript; available in PMC 2015 December 10.

Table 4

Association of *Salmonella* Typhimurium Multilocus Sequence Type, Human Immunodeficiency Virus Infection, and Multidrug Resistance (Resistance to ≥3 Antimicrobials)

***Salmonella* Typhimurium Sequence Type (n = 97)**	**HIV-Uninfected Patients (n = 7)**	**HIV-Infected Patients (n = 38)**	**Nonresistant Isolates or Isolates With Limited Resistance**	**Multidrug-Resistant Isolates[a]**
16 (n = 1)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
19 (n = 30)	4 (28.6)	10 (71.4)	21 (70.0)	9 (30.0)
302 (n = 1)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
313 (n = 65)	1 (3.4)	28 (96.6)	17 (26.1)	48 (73.8)

Data are presented as No. (%).

Abbreviation: HIV, human immunodeficiency virus.

[a] Includes intermediate resistance.