Clinical and microbiological features of invasive nontyphoidal Salmonella associated with HIV-infected patients, Gauteng Province, South Africa

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Abstract
The aim of this study was to define factors associated with HIV-infected versus uninfected patients with invasive nontyphoidal Salmonella (iNTS) and factors associated with mortality, which are inadequately described in Africa.

Laboratory-based surveillance for iNTS was undertaken. At selected sentinel sites, clinical data (age, sex, HIV status, severity of illness, and outcome) were collected.

Surveillance was conducted in Gauteng, South Africa, from 2003 to 2013. Clinical and microbiological differences between HIV-infected and uninfected patients were defined and risk factors for mortality established.
Of 4886 iNTS infections in Gauteng from 2003 to 2013, 3106 (63.5%) were diagnosed at sentinel sites. Among persons with iNTS infections, more HIV-infected persons were aged ≥5 years ($\chi^2 = 417.6; P < 0.001$) and more HIV-infected children were malnourished ($\chi^2 = 5.8; P = 0.02$). Although 760 (30.6%) patients died, mortality decreased between 2003 [97/263 (36.9%)] and 2013 [926/1200 (21.7%)]. On univariate analysis, mortality was associated with patients aged 25 to 49 years [odds ratio (OR) = 2.2; 95% confidence interval (CI) = 1.7–2.7; $P < 0.001$ and ≥50 years [OR = 3.0; 95% CI = 2.2–4.1; $P < 0.001$] compared with children < 5 years, HIV-infected patients [OR = 2.4; 95% CI = 1.7–3.4; $P < 0.001$], and severe illness [OR = 5.4; 95% CI = 3.6–8.1; $P < 0.001$]. On multivariate analysis, mortality was associated with patients aged ≥50 years [adjusted OR (AOR) = 3.6, 95% CI = 2.1–6.1, $P < 0.001$] and severe illness (AOR = 6.3; 95% CI = 3.8–10.5; $P < 0.001$).

Mortality due to iNTS in Gauteng remains high primarily due to disease severity. Interventions must be aimed at predisposing conditions, including HIV, other immune-suppressive conditions, and malignancy.

Abbreviations: AOR = Adjusted odds ratio, ART = Antiretroviral therapy, CDW = Central Data Warehouse, CED = Centre for Enteric Diseases, CI = Confidence interval, ESBL = Extended-spectrum beta lactamase, FERG = Foodborne diseases Epidemiology Reference Group, HIV = Human immunodeficiency virus, iNTS = Invasive nontyphoidal Salmonella, MDR = Multidrug resistance, MIC = Minimum inhibitory concentrations, NHLS = National Health Laboratory Service, OR = Odds Ratio, PBS = Pitt bacteremia score, PEM = Protein energy malnutrition, TSAP = Typhoid fever surveillance in Africa program.

Keywords: AIDS, HIV, invasive nontyphoidal Salmonella, malnutrition, mortality, severity of illness, South Africa
mortality due to iNTS, we calculated odds ratios (ORs), 95% confidence intervals (CIs), and P values for age group, sex, HIV status, PBS, other comorbidities, serotype, MDR, and ESBL production. For multivariate analysis, we used logistic regression to calculate adjusted ORs (AORs). Patients with missing data were excluded from the analyses. The \( \chi^2 \) test was used to compare clinical and microbiological features of HIV-uninfected with HIV-infected patients with iNTS. Two-sided P values of < 0.05 were considered significant for all analyses. All statistical analyses were performed using STATA (College Station, Texas, USA) version 13 software.

2.3. Ethical review

Ethics approvals were obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC) (M110601, granted June 24, 2011).

3. Results

We recorded 4886 laboratory-confirmed iNTS infections in Gauteng Province from January 2003 to December 2013, of which 334 (6.8%) were identified using CDW data. Of 4728 (96.8%) iNTS-infected patients for whom sex was recorded, 2478 (52.4%) were male; 4661 (95.4%) patients had age recorded, ranging from 0 days (newborn) to 93 years, with a median of 32 years (Fig. 1). The highest incidence of iNTS infection was in children aged < 5 years, averaging 10.9 per 100,000 population per year during 2003 to 2013. The lowest incidence rate was in children aged 5 to 14 years (averaging 0.9 per 100,000 population per year).

Serotyping was completed on 4459 Salmonella isolates: the most common serotypes were Salmonella enterica serovar Typhimurium (Salmonella Typhimurium) [2469 (55.4%)]; Salmonella Enteritidis [1156 (25.9%)]; Salmonella Isangi [175 (3.9%)]; and Salmonella Dublin [170 (3.8%)]. Antimicrobial susceptibility testing results were available for 4347 (97.5%) isolates: 1035 (23.8%) isolates were MDR, of which 381 (36.8%) were ESBL producers (Table 1).

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Table 1

| Serotype and number of isolates tested (n) | Ampicillin n (%) | Chloramphenicol n (%) | Trimethoprim-Sulfamethoxazole n (%) | Tetracycline n (%) | Ciprofloxacin intermediate n (%) | Ciprofloxacin resistant n (%) | Ceftriaxone n (%) | ESBL producers n (%) | Multidrug resistance n (%) |
|------------------------------------------|-----------------|-----------------------|------------------------------------|-------------------|---------------------------------|---------------------------|----------------------|----------------------|--------------------------|
| Typhimurium (n=2420)                     | 1651 (68.2)     | 933 (38.6)            | 1491 (61.6)                        | 1048 (43.3)       | 784 (32.4)                      | 63 (2.6)                  | 232 (9.5)            | 324 (13.4)           | 806 (33.3)               |
| Enteritidis (n=1149)                     | 43 (3.7)        | 30 (2.6)              | 38 (3.9)                           | 127 (11.1)        | 344 (29.9)                      | 5 (0.4)                   | 6 (0.5)              | 7 (0.6)              | 20 (1.7)                 |
| Isangi (n=171)                           | 165 (96.5)      | 163 (95.3)            | 157 (91.8)                         | 167 (97.7)        | 130 (76.0)                      | 7 (4.1)                   | 113 (66.1)           | 104 (60.4)           | 155 (90.6)               |
| Dublin (n=166)                           | 5 (3.0)         | 5 (3.0)               | 6 (3.0)                            | 5 (3.0)           | 3 (1.8)                         | 0 (0.0)                   | 0 (0.0)              | 1 (0.6)              |                          |
| Other (n=441)                            | 138 (31.3)      | 91 (20.6)             | 144 (32.7)                         | 167 (37.9)        | 56 (12.7)                       | 11 (2.5)                  | 41 (9.3)             | 39 (8.8)             | 51 (11.6)                |
| Total (n=4347)                           | 2002 (46.1)     | 1222 (28.1)           | 1836 (42.2)                        | 1514 (34.8)       | 1137 (26.2)                     | 86 (1.9)                  | 392 (9.0)            | 474 (10.9)           | 1035 (23.8)              |

ESBL = extended-spectrum \( \beta \)-lactamase.
3.2. HIV-infected versus HIV-uninfected patients

Among persons infected with iNTS, comparing clinical features of HIV-uninfected with HIV-infected individuals, there were significant differences in age range: a significantly smaller proportion of HIV-infected patients were aged <5 years (HIV-infected: 256/1896 (13.5%) vs HIV-uninfected: 170/258 (65.9%); \( \chi^2 = 417.6; P < 0.001 \)) (Table 2). HIV-infected individuals were less likely to present with nosocomially acquired iNTS infection [HIV-infected: 235/1881 (12.5%) vs HIV-uninfected: 59/253 (23.3%); \( \chi^2 = 22.0; P < 0.001 \)] and were less likely to have other comorbid conditions [HIV-infected: 302/1898 (15.9%) vs HIV-uninfected: 96/258 (37.2%); \( \chi^2 = 68.4; P < 0.001 \)] (Table 2). HIV-infected patients presenting with iNTS were also more likely to be diagnosed with PEM [HIV-infected: 81/322 (25.2%) vs HIV-uninfected: 29/182 (15.9%); \( \chi^2 = 5.8; P = 0.02 \)]. Among persons infected with iNTS, there was no significant difference, however, between severity of illness (PBS score \( \geq 4 \)) between the 2 groups [HIV-infected: 79/1415 (5.6%) vs HIV-uninfected: 9/204 (4.4%); \( \chi^2 = 0.5; P = 0.5 \)] (Table 2). HIV-infected patients were also more likely to present with invasive Salmonella Typhimurium than other serotypes [HIV-infected: 1110/1773 (62.6%) vs HIV-uninfected: 73/232 (31.5%); \( \chi^2 = 118.0; P < 0.001 \)] or to present with MDR Salmonella isolates [HIV-infected: 491/1753 (28.0%) vs HIV-uninfected: 38/224 (16.9%); \( \chi^2 = 12.4; P < 0.001 \)] (Table 2). HIV-infected individuals were less likely to be infected with invasive Salmonella Enteritidis [HIV-infected: 422/1773 (23.8%) vs HIV-uninfected: 76/232 (32.8%); \( \chi^2 = 8.8; P = 0.003 \)].

3.3. Risk factors for mortality

Complete clinical and microbiological data were available for 1448 of 2481 (59.9%) patients for mortality analysis. On univariate analysis, mortality among persons with iNTS infection was associated with patients aged 25 to 49 years compared with children aged <5 years (OR = 2.2; 95% CI = 1.7–2.7; P < 0.001) and with those \( \geq 50 \) years of age compared with children aged <5 years (OR = 3.0; 95% CI = 2.2–4.1; P < 0.001), HIV-infected patients (OR = 2.4; 95% CI = 1.7–3.4; P < 0.001) compared with HIV-uninfected patients, more severe illness (PBS \( \geq 4 \)) (OR = 5.4; 95% CI = 3.6–8.1; P < 0.001), and infection with a MDR Salmonella (OR = 1.9; 95% CI = 1.5–2.3; P < 0.001) (Table 3). On multivariate analysis, mortality among iNTS-infected persons was associated with patients \( \geq 50 \) years of age [adjusted OR

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**Table 2**

| HIV uninfected | HIV infected | Total | \( \chi^2 \) | \( P \) |
|----------------|--------------|-------|-------------|--------|
| Sex            |              |       |             |        |
| Male           | 147 (9.4)    | 963 (61.3) | 1110 | 4.1 | 0.04 |
| Female         | 107 (7.4)    | 920 (63.6) | 1027 | — | — |
| Unknown        | 4 (0.6)      | 17 (11.9)  | 21 | — | N/A |
| Age (y)        |              |         |             |        |
| <5             | 170 (27.4)   | 256 (41.4) | 426 | 417.6 | <0.001 |
| 5–14           | 12 (11.1)    | 66 (61.1)  | 78 | — | — |
| 15–24          | 10 (6.0)     | 106 (63.9) | 116 | — | — |
| 25–49          | 40 (2.3)     | 125 (73.6) | 165 | — | — |
| \( \geq 50 \)   | 26 (7.5)     | 181 (54.2) | 207 | — | — |
| Unknown        | 0 (0.0)      | 4 (1.3)   | 4 | — | N/A |
| Protein energy malnutrition (children <15 y) |              |         |             |        |
| No             | 153 (23.9)   | 241 (47.2) | 394 | 51.8 | 0.02 |
| Yes            | 20 (23.4)    | 81 (65.3)  | 101 | — | — |
| Unknown        | 0 (0.0)      | 0 (0.0)   | 0 | — | N/A |
| Salmonella serotype |              |         |             |        |
| Typhimurium    | 73 (4.3)     | 1410 (61.7) | 1483 | 118.0 | <0.001 |
| Enteritidis    | 76 (11.1)    | 422 (61.7) | 498 | — | — |
| Isangi         | 18 (15.8)    | 46 (40.3)  | 64 | — | — |
| Dublin         | 10 (8.3)     | 66 (64.6)  | 76 | — | — |
| Other serotypes | 55 (16.1) | 120 (65.8) | 175 | — | — |
| Unknown        | 26 (11.4)    | 127 (55.7) | 153 | — | — |
| Salmonella multidrug resistance |              |         |             |        |
| No             | 186 (8.9)    | 1262 (60.4) | 1448 | 12.4 | <0.001 |
| Yes            | 38 (5.3)     | 491 (68.5) | 529 | — | — |
| Unknown        | 34 (11.3)    | 147 (40.0) | 181 | — | N/A |
| Salmonella ESBL production |              |         |             |        |
| No             | 201 (8.2)    | 1529 (62.2) | 1730 | 1.1 | 0.3 |
| Yes            | 23 (6.6)     | 224 (64.1) | 247 | — | — |
| Unknown        | 34 (11.3)    | 147 (40.0) | 181 | — | N/A |

Statistical analyses refer only to those patients for whom clinical features and HIV status was known. ESBL = Extended-spectrum \( \beta \)-lactamase.

Includes all cases, including those for whom HIV status was unknown.
(AOR) = 3.6, 95% CI = 2.1–6.1, \( P < 0.001 \), PBS ≥4 (AOR = 6.3; 95% CI = 3.8–10.5; \( P < 0.001 \), and infection with MDR Salmonella (AOR = 1.7, 95% CI = 1.2–2.3, \( P = 0.001 \)), but not associated with being HIV-infected (AOR = 1.4; 95% CI = 0.9–2.3; \( P = 0.2 \)) (Table 3). Analyzing data on PEM in children, these patients were not significantly more likely to die than children who did not have PEM (OR = 1.5; 95% CI = 1.0–2.4; \( P = 0.07 \)) (Table 3). Among HIV-infected patients, those with CD4+ counts ≤350 were significantly more likely to die (OR = 0.4; 95% CI = 0.2–0.7; \( P = 0.004 \)), but a history of ART use did not significantly impact outcome (OR = 0.8; 95% CI = 0.6–1.1, \( P = 0.1 \)).

Reviewing information on antimicrobial management of patients, 2138 of 3106 (68.8%) of all sentinel site patients and 575 of 760 (75.7%) of patients who died had data collected. Individual review of clinical case report forms revealed inconsistent data collection regarding prescribing and administration of antimicrobials. Many patients were prescribed multiple antibiotics and prescriptions were changed during the admission.

4. Discussion

Invasive salmonellosis remains a challenge in Africa, due to a number of significant predisposing factors, including malaria, PEM in children, and HIV infection.\(^{[14,15]}\) In South Africa, the major contributing factor to invasive salmonellosis is HIV infection.\(^{[16]}\) However, factors associated with mortality in

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**Table 3**

| Characteristic                  | Cases n | Deaths n | CFR (%) | Univariate analysis | Multivariate analysis\(^1\) |
|--------------------------------|---------|----------|---------|--------------------|---------------------------|
| Sex                            |         |          |         |                    |                           |
| Male                           | 1301    | 416      | 32.0    | —                  | —                         |
| Female                         | 1156    | 334      | 28.9    | 0.9 0.7–1.0 0.1    | 0.8 0.6–1.1 0.2           |
| Age, y                         |         |          |         |                    |                           |
| <5                             | 534     | 101      | 18.9    | —                  | —                         |
| 5–14                           | 90      | 25       | 27.8    | 1.6 1.0–2.7 0.06   | 1.4 0.6–3.3 0.4           |
| 15–24                          | 132     | 34       | 25.8    | 1.5 1.0–2.3 0.08   | 1.8 0.9–3.5 0.1           |
| 25–49                          | 1435    | 480      | 33.5    | 2.2 1.7–2.7 <0.001 | 2.7 1.7–4.2 <0.001       |
| ≥50                            | 287     | 118      | 41.1    | 3.0 2.2–4.1 <0.001 | 3.6 2.1–6.1 <0.001       |
| HIV status                     |         |          |         |                    |                           |
| Uninfected                     | 255     | 41       | 16.1    | —                  | —                         |
| Infected                       | 1811    | 572      | 31.6    | 2.4 1.7–3.4 <0.001 | —                         |
| Pitt bacteremia (severity of illness) score |         |          |         |                    |                           |
| <4                             | 1731    | 460      | 26.6    | —                  | —                         |
| ≥4                             | 109     | 72       | 66.1    | 5.4 3.6–8.1 <0.001 | 6.3 3.8–10.5 <0.001      |
| Nosocomial infection           |         |          |         |                    |                           |
| No                             | 2099    | 639      | 30.4    | —                  | —                         |
| Yes                            | 355     | 112      | 31.5    | 1.1 0.8–1.3 0.7    | —                         |
| Other comorbid conditions      |         |          |         |                    |                           |
| No                             | 1679    | 506      | 30.1    | —                  | —                         |
| Yes                            | 427     | 132      | 30.2    | 1.0 0.8–1.3 1.0    | —                         |
| Protein energy malnutrition (children <14 y)\(^6\) |         |          |         |                    |                           |
| No                             | 503     | 96       | 19.1    | —                  | —                         |
| Yes                            | 124     | 33       | 26.6    | —                  | —                         |
| CD4+ count (HIV-infected patients only)\(^7\) |         |          |         |                    |                           |
| CD4+ ≤350                      | 1193    | 365      | 30.6    | —                  | —                         |
| CD4+ >350                      | 94      | 15       | 16.0    | —                  | —                         |
| Antiretroviral treatment (HIV-infected patients only)\(^8\) |         |          |         |                    |                           |
| No                             | 1106    | 389      | 27.7    | —                  | —                         |
| Yes                            | 287     | 66       | 23.0    | —                  | —                         |
| Salmonella serotype            |         |          |         |                    |                           |
| Typhimurium                    | 1,329   | 465      | 35.0    | —                  | —                         |
| Enteritidis                    | 567     | 137      | 24.2    | 0.5 0.5–0.7 <0.001 | 0.8 0.6–1.1 0.2           |
| Isangi                         | 84      | 30       | 35.7    | 1.0 0.7–1.6 0.9    | 1.7 0.8–3.9 0.2           |
| Dublin                         | 94      | 20       | 21.3    | 0.5 0.3–0.8 0.008  | 0.5 0.2–1.1 0.07          |
| Other serotypes                | 224     | 108      | 26.5    | 0.8 0.6–1.1 0.2    | 1.3 0.8–2.1 0.3           |
| Salmonella multidrug resistance|         |          |         |                    |                           |
| No                             | 1678    | 464      | 27.7    | —                  | —                         |
| Yes                            | 588     | 245      | 41.7    | 1.9 1.5–2.3 <0.001 | 1.7 1.2–2.3 0.001        |
| Salmonella ESBL production\(^9\) |         |          |         |                    |                           |
| No                             | 1995    | 606      | 30.4    | —                  | —                         |
| Yes                            | 271     | 103      | 38.0    | 1.4 1.1–1.8 0.01   | —                         |

Complete data were available for 1448 (59.9%) patients for mortality analysis.

AOR = adjusted odds ratio, CI = confidence interval, ESBL = Extended-spectrum \( \beta \)-lactamase, OR = odds ratio.

\(^{6}\) Excluded from multivariate analysis: multivariate analysis includes all age groups; multidrug resistance includes ESBL producing isolates.

\(^{7}\) Excluded from multivariate analysis: multivariate analysis includes both HIV-infected and HIV-uninfected patients.
patients infected with iNZ were not previously been well described.

We examined disease burdens of iNZ in the predominantly urbanized population of Gauteng between 2003 and 2013, recording a significant decrease in the numbers of iNZ cases, following the roll out of ART in 2004. Incidence for iNZ was highest among children aged <5 years and adults aged 25 to 49 years, highlighting the vulnerability of the former and the predominance of HIV-associated infections in the latter, supporting data from previous studies and systematic analyses. Similar to other African studies, the predominant serotypes were Salmonella Typhimurium and Salmonella Enteritidis. We additionally identified increased numbers of Salmonella Isangi and Salmonella Dublin. Salmonella Enteritidis and Salmonella Dublin isolate were predominantly susceptible to the antimicrobials tested, but in common with other African studies, MDR was common in Salmonella Typhimurium and Salmonella Enteritidis, respectively. Conversely, reports from Mali indicate that MDR occurred in >90% and 40% of Salmonella Typhimurium and Salmonella Enteritidis, respectively. Interestingly, MDR was low in Salmonella Dublin in Mali, similar to our findings. The predominance of Salmonella Typhimurium and Salmonella Enteritidis in Africa has highlighted these pathogens as primary serotypes for Salmonella vaccine development. Rapidly burgeoning MDR is making vaccine development an important imperative.

There were additional differences between HIV-infected and HIV-uninfected individuals presenting with iNZ. Children aged less than 5 years with iNZ infections were less likely to be HIV infected. In addition, more HIV-uninfected patients with iNZ had comorbidities including chronic organ failure or malignancy, highlighting noncommunicable diseases as potential risk factor for iNZ infection. Although HIV-uninfected patients presented more frequently with nosocomial-acquired iNZ infections, this study did not examine the role of HIV clinics in patients with iNZ. Data on long-term care facilities were also not always forthcoming; thus, this finding may not be truly reflective, as some HIV-infected patients in particular may have acquired iNZ while in these care facilities. Nosocomial salmonellosis is well described in South Africa, often affecting children and nonetheless warrants careful monitoring. In contrast to invasive shigellosis, we did not see an excess of adult women presenting with iNTS; intrinsic characteristics of Salmonella, in HIV-infected patients in particular, appear to be at play in the context of invasive disease, beyond human behavioral factors. This has already been shown for Salmonella Typhimurium ST313 and Salmonella Enteritidis. Further differences between HIV-infected versus uninfected individuals included Salmonella serotype: a significantly higher proportion of HIV-uninfected individuals presented with invasive Salmonella Enteritidis. This lesser association of Salmonella Enteritidis with HIV infection may partly explain why mortality due to this pathogen was significantly lower than Salmonella Typhimurium. This contrasts with observations of Tapia et al., who found a significantly higher case fatality of 27.8% associated with Salmonella Enteritidis than Salmonella Typhimurium in Mali, possibly in relation to a highly virulent clone in that country. HIV-infected patients in our series were more likely to be infected with multidrug-resistant pathogens. This could be ascribed to their multiple exposures to antibiotics associated with management of other opportunistic infections. Severity of illness (PFS >4), however, was comparable between the 2 groups: irrespective of the primary illness, immune-suppressive conditions predispose patients to iNZ.

Other researchers have highlighted the importance of underlying immunosuppressive disease, other than HIV, as the most important risk factor in adult patients for iNZ. Older patients, neonates, and isolation of invasive serotypes were identified as risk factors for iNZ infection in HIV-uninfected patients. Malaria and malnutrition are important risk factors for iNZ in children. The excessive numbers of children in our series with iNZT who were HIV-infected with PEM is concerning. HIV infection has been associated with undernourishment in children aged <5 years in South Africa, and clearly remains problematic. This may be directly due to an HIV-associated effect in our study or due to other factors such as maternal illness or death. This may also be indicative of ongoing failures in nutritional programs in primary health care. Feasey et al. have clearly shown that iNZT rates decrease when childhood nutrition programs are introduced and a greater emphasis may be needed on such programs in South Africa.

We elected to analyze data for children aged less than 5 years separately from those aged 5 to 14 years to correspond to incidence data that have been calculated for iNTS and ART programs in Gauteng Province, South Africa. First, the younger group is predisposed to higher mortality due to foodborne diseases, including salmonellosis. Second, differences in the HIV rates and presentation with iNZ between these 2 age groups may impact analyses: HIV-infected children surviving beyond 5 years of age was an unusual observation before the ART roll-out. Many of these patients in our series had associated malignancies or other predisposing immune-suppressive conditions as opposed to HIV infection. We have shown that iNZ incidence rates in children aged <5 years correlate poorly with ART treatment programs.

We characterized risk factors for mortality due to iNZ, with a view to highlighting interventions to decrease mortality rates. Mortality among persons infected with iNZ has decreased significantly after the introduction of ART, in other African studies and we have observed a similar trend, but clinical risk factors needed clarification. HIV infection on univariate analysis, and severity of illness (PFS >4), adults ≥25 years, and isolation of MDR Salmonella on multivariate analysis, were associated with excessive mortality. Older age and disease severity were the most significant predictors of a poor outcome. Excessive mortality occurs in patients with severely immunosuppressive conditions predisposing to iNZ, besides HIV infection, including malignancy, organ failure, and prematurity. In HIV-infected persons, we found that mortality was associated with patients with a low CD4+ count, who also bore the greatest burden of illness, but not with ART use, supporting global initiatives for earlier initiation of ART.

This study had some limitations. First, although we attempted to comprehensively identify the majority of the Gauteng iNZT cases during the study period, it is possible that some were not identified by our surveillance system, which focused primarily on patients presenting to public hospitals. Indications and use of blood cultures are unlikely to have changed over the period, however, and the majority of cases (~60%) were identified in
sentinel surveillance hospitals. This study also did not look at the impact of delayed or inappropriate antimicrobial therapy on mortality, as these data were not sufficiently or were inconsistently collected and over 30% of patients died within 48 hours of admission, before culture results and susceptibilities would have become available. Complete clinical information was not available for all cases at sentinel hospitals, but total case numbers were large. This should minimize the effect on the statistical analysis. Similarly, missing isolates constituted <10% of those characterized; we believe that the serotyping and drug resistance data are representative and it is unlikely those iNTS cases that were identified on audit would have significantly altered our findings.

In conclusion, we showed although mortality due to iNTS in South Africa has decreased, it remains high irrespective of the patients’ HIV status. We additionally noted a concerning increase in invasive cases of Salmonella Enteritidis across all age groups,[11] for reasons that are not well understood and needing further elucidation. These observations, in combination with the prevalence of multidrug-resistant Salmonella Typhimurium in Africa, support the need for the development of vaccines for these serotypes. As ART becomes more readily available in South Africa, with more patients and older patients accessing antiretroviral programs, we may see a change in disease patterns of iNTS to more closely resemble those of the developed world.[15]

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