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Correlates of non-typhoidal *Salmonella* bacteraemia: A case–control study

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ABSTRACT

Objective: Limited up-to-date evidence exists on host-related characteristics of non-typhoidal *Salmonella* (NTS) bacteraemia in high-income countries. Correlates of NTS bacteraemia in Israel were examined in this study.
Methods: A case–control study was conducted using the medical records of patients hospitalized with NTS bacteraemia in Jerusalem during 1997–2016 ($n = 106$; 57 children, 49 adults). Two control groups were included: (1) randomly selected controls ($n = 101$), who were patients hospitalized due to bacteraemia with other pathogens; (2) patients with salmonellosis without bacteraemia ($n = 112$). Age-stratified logistic regression models were constructed.
Results: In children, a recent emergency room visit was associated with an increased likelihood of NTS bacteraemia. In adults, the likelihood of NTS bacteraemia versus salmonellosis increased in relation to Charlson comorbidity score (adjusted odds ratio (aOR) 1.29, 95% confidence interval (CI) 1.00–1.66, for each 1-point increase in the score), while an inverse association was found with haemoglobin level (aOR 0.72, 95% CI 0.54–0.95). Steroid therapy increased the likelihood of NTS bacteraemia compared to patients with bacteraemia due to other pathogens (aOR 5.22, 95% CI 1.01–26.93).
Conclusions: In children, NTS bacteraemia was probably present at their prior emergency room visit. A high comorbidity burden increased the likelihood of bacteraemia in adults with *Salmonella* infection, while haemoglobin level might be protective.

Introduction

The genus *Salmonella* comprises *Salmonella enterica* and *Salmonella bongori*. *Salmonella enterica* subspecies I includes nearly all pathogenic serotypes for humans. The growth of *S. enterica* Typhi and *S. enterica* Paratyphi is limited to humans, and these organisms cause enteric fever (Pegues and Miller, 2015). Non-typhoidal *Salmonella* (NTS) cause acute gastroenteritis – salmonellosis (Pegues and Miller, 2015; Hohmann, 2001) – a foodborne disease that is prevalent worldwide.

Salmonellosis is generally a self-limited disease characterized by diarrhoea and vomiting, but a severe illness may occur in young children, the elderly, and the immunocompromised (Pegues and Miller, 2015; Hohmann, 2001). NTS species can cause bacteraemia and some patients develop localized infections in organs outside the intestine (Pegues and Miller, 2015; Hohmann, 2001). In HIV high-prevalence regions, the incidence of invasive NTS disease is highest among infants and young adults (Ao et al., 2015), while in HIV low-prevalence countries, young children and the elderly are the high-risk groups (Ao et al., 2015). The incidence of NTS bacteraemia is increasing, especially in Sub-Saharan Africa (Ao et al., 2015; Gordon et al., 2001; Bronzan et al., 2007; Feasey et al., 2012), where HIV infection and malnutrition are common (Feasey et al., 2012). NTS has been reported to be among the most common causes of bacteraemia in such settings (Bronzan et al., 2007; Feasey et al., 2012; Sothmann et al., 2015), mostly without symptoms of gastroenteritis (Feasey et al., 2012). In developed countries, and even in less-developed regions, NTS bacteraemia occurs in persons with immunosuppression and chronic comorbidities (Hohmann, 2001; Brown and Eykyn, 2000; Galofre et al., 1994; Yombi et al., 2015; Matheson et al., 2010).

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In Israel, as in many developed countries, non-communicable diseases are the leading causes of death (Muhsen et al., 2017). On the other hand, salmonellosis remains endemic in Israel, despite a decrease in the disease incidence over the past decade (Bassal et al., 2012). An analysis of *Salmonella* isolates submitted to the reference laboratory in Israel between 1996 and 2006, showed 3.7% extra-intestinal isolates, mostly (74.1%) recovered from blood (Zaidenstein et al., 2010).

New vaccines against NTS are under development (MacLennan et al., 2014). While the need for such vaccines is obvious for populations in Sub-Saharan Africa, where the invasive NTS disease in endemic and case-fatality is high, vaccines against NTS in developed countries will likely be relevant to specific high-risk groups. However, limited up-to-date evidence exists on the correlates for NTS bacteraemia in developed countries. The aim of this study was to examine correlates of NTS bacteraemia in comparison to salmonellosis without bacteraemia and compared to bacteraemia due to other pathogens.

Methods

Study population and design

A retrospective case–control study was conducted using the medical records of patients hospitalized at Shaare Zedek Medical Centre during 1997–2016. This 1000-bed teaching hospital serves the Jewish and Arab population of Jerusalem and surrounding area.

Cases were all patients hospitalized with NTS bacteraemia. Two control groups were included: one consisted of all patients hospitalized for salmonellosis without bacteraemia, and the other included patients who were hospitalized for bacteraemia due to other pathogens, excluding patients with possible contaminants (i.e., coagulase-negative staphylococci, viridans group streptococci). To increase the specificity of the bacteraemia definition, only patients with a bacterial blood isolate and clinical course consistent with the bacteraemia were included in the study. These controls were randomly selected among all bacteraemia cases and were matched with cases on age (grouped as <1, 1–4, 5–18, 19–59, 60–97 years), sex, and year of admission. The rationale behind using the control group of salmonellosis patients was to identify correlates of NTS bacteraemia beyond the risk of *Salmonella* infection. The rationale behind using control patients with bacteraemia due to other pathogens was to identify correlates of NTS bacteraemia beyond the propensity of bacteraemia. The main study hypothesis was that background morbidity and immunosuppression would be more common among the NTS bacteraemia patients than among the controls.

Information obtained included demographic characteristics (age at admission and sex), hospitalizations and emergency room visits in the 2 weeks prior to admission, antibiotic use in the past week, antibiotic therapy received during admission, and the microbiological characteristics of the NTS bacteraemia isolates (serotypes and antibiotic resistance profiles). Data on background illnesses (e.g., diabetes mellitus, heart disease, stroke, cancer, renal failure, atrial fibrillation) were collected and the Charlson comorbidity score (CCS) (Charlson et al., 1987) was calculated. CCS was analysed as a discrete variable.

Data analysis

The Chi-square test or Fisher's exact test, as appropriate, was used to examine differences between cases and controls in categorical demographic and clinical variables. The Mann–Whitney test was used to examine differences in age and CCS between two groups. Multivariable logistic regression models were fitted. In one analysis, the control group included patients with salmonellosis and in the other the control group included patients hospitalized for bacteraemia due to other pathogens. Unadjusted and adjusted odds ratios (OR, aOR) and 95% confidence intervals (CI) were obtained from these models. Given differences in the distribution of underlying conditions for invasive NTS disease between children and adults (Shimoni et al., 1999), the data analysis was performed separately for children aged ≤18 years and adults aged >18 years. Multicollinearity between the independent variables was assessed using the variance inflation factor (VIF). A two-sided $p < 0.05$ was considered significant. Adjustment for multiple comparisons was done by Benjamini–Hochberg false discovery rate method (Benjamini and Hochberg, 1995). Data were analysed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) and Winpepi (Abramson, 2011).

Results

Data for 319 patients aged 0–97 years who were admitted to the hospital between January 1997 and June 2016 were analysed: 106 patients with NTS bacteraemia (52% male), 112 control patients with salmonellosis (46% male), and 101 control patients with bacteraemia due to other pathogens (51% male). The bacteraemia control group included patients with the following blood isolates: *Escherichia coli* (32%), *Klebsiella pneumoniae* (6%), *Haemophilus influenzae* (5%), *Campylobacter* (3%), *Streptococcus pneumoniae* (28%), *Staphylococcus aureus* (11%), group B *Streptococcus* (3%), and other bacteria (12%).

Of the NTS bacteraemia cases, 19% were children aged less than 1 year, 27% were children aged 1–4 years, and 8% were children aged 5–18 years, while adults aged 19–59 years comprised 10% and those aged 60–97 years comprised 36% of the cases.

Correlates of NTS bacteraemia in patients aged ≤18 years

A significantly higher percentage of NTS bacteraemia cases (59%) had visited the emergency room 2 weeks before hospitalization compared to salmonellosis patients (9%) and patients with bacteraemia due to other pathogens (8%) ($p < 0.001$). An emergency room visit due to viral infection (based on clinical (syndromic) judgement and documentation in the medical records) in the 2 weeks prior to hospitalization was documented in 21% of the cases compared to 0–1% of the control groups ($p < 0.001$). An emergency room visit due to gastroenteritis was recorded in 11% of the cases compared to 7% in salmonellosis patients ($p = 0.9$), but none of the patients with bacteraemia due to other pathogens had a similar emergency visit ($p < 0.001$). Cases less often had surgical or invasive procedures during hospitalization than patients with bacteraemia due to other pathogens (9% vs. 28%, $p = 0.008$). The percentage of NTS bacteraemia patients who had received antibiotics 1 week prior to hospitalization was higher than the percentage of patients with bacteraemia due to other pathogens who had received antibiotics (26% vs. 11%) ($p = 0.031$). NTS bacteraemia patients had lower mean haemoglobin levels at admission than patients with salmonellosis ($p = 0.009$), but no significant difference was noted compared to patients with bacteraemia due to other pathogens ($p = 0.4$) (Table 1). Chronic underlying conditions were uncommon (0–5%) in children (Supplementary material, Table S1).

In the multivariable analysis, the only factor associated with NTS bacteraemia in children was an emergency room visit during the 2 weeks prior to hospitalization: aOR 16.08 (95% CI 5.77–44.86) compared to patients with salmonellosis. Compared to children with bacteraemia due to other pathogens, the association with a recent emergency room visit retained significance (aOR 17.57, 95% CI 5.36–57.57), as well as the inverse association with surgery/

Table 1
Comparison of clinical characteristics between the study groups in patients aged ≤18 years.[a]

	NTS bacteraemia $n=57$	Salmonellosis $n=82$	Other bacteraemia $n=65$	p-Value 1	p-Value 2
Hospitalization in the past 2 weeks	7 (13%)	6 (7%)	3 (5%)	0.3	0.11
Emergency room visit in the past 2 weeks	33 (59%)	7 (9%)	5 (8%)	<0.001[b]	<0.001[b]
Emergency room visit in the past 2 weeks for gastroenteritis	6 (11%)	6 (7%)	0 (0%)	0.5	0.007[b]
Emergency room visit in the past 2 weeks for viral infection[d]	12 (21%)	1 (1%)	0 (0%)	<0.001[b]	<0.001[b]
Antibiotic therapy in the past week	14 (26%)	14 (17%)	7 (11%)	0.2	0.031[c]
Current surgery/invasive procedure	5 (9%)	5 (6%)	18 (28%)	0.5	0.008[b]
Mean haemoglobin (SD), g/dl[e]	11.5 (1.6)	12.3 (2.0)	11.7 (2.1)	0.009[b]	0.4

NTS, non-typhoidal *Salmonella*; SD, standard deviation.
[a] p-Value 1 for the comparison between NTS bacteraemia cases and patients with salmonellosis; p-value 2 for the comparison between NTS bacteraemia cases and patients with bacteraemia due to other pathogens. The p-value was obtained by Chi-square test or Fisher's exact test, as appropriate, for all comparisons, with the exception of haemoglobin levels, for which the Student t-test was used.
[b] After correction for multiple comparisons, $p<0.05$.
[c] After correction for multiple comparisons, $p=0.054$.
[d] Viral infection was defined based on syndromic judgement and documentation in the medical records.
[e] Information on haemoglobin was missing for five NTS bacteraemia cases, two patients with salmonellosis, and four patients with bacteraemia due to other pathogens.

invasive procedure during the current hospitalization (aOR 0.13, 95% CI 0.03–0.59) (Table 2).

Correlates of NTS bacteraemia in patients aged >18 years

Adult NTS bacteraemia cases had a significantly higher mean CCS ($p=0.004$) and lower mean haemoglobin level at admission ($p=0.011$) than patients with salmonellosis, but not when compared to patients with bacteraemia due to other pathogens ($p=0.9$) (Table 3). Cases had a history of steroid therapy more often than patients with bacteraemia due to other pathogens (20% vs. 6%, $p=0.05$). Cases had atrial fibrillation and dependent functional status more often than both control groups (Table 3).

In the multivariable analysis, compared to patients with salmonellosis, the likelihood of NTS bacteraemia was increased by 29% for each 1-point increase in CCS (aOR 1.29, 95% CI 1.00–1.66), while an inverse association was observed for NTS bacteraemia and haemoglobin level at admission (aOR 0.72, 95% CI 0.54–0.95). A second model that included the variable cancer instead of CCS showed a 7.5-fold higher likelihood of NTS bacteraemia in patients with cancer versus those without cancer ($p=0.07$), and a positive association with atrial fibrillation (aOR 14.26, 95% CI 1.35–150.68). Steroid therapy remained significantly related to NTS bacteraemia when compared to patients with bacteraemia due to other pathogens (Table 4). In additional models, the variable 'dependent functional status' was assessed but showed no significant associations with NTS bacteraemia ($p=0.19$), therefore it was excluded from the model.

In all models, VIF values ranged between 1 and 1.8, suggesting no multicollinearity.

Microbiological characteristics of NTS bacteraemia

Salmonella serogroups B, C, and D were detected in 19%, 32%, and 49%, respectively, of the NTS bacteraemia cases. Information on the serotype was available for 34 blood isolates: 13 (38%) were *S. enterica* Enteritidis, seven (21%) were *S. enterica* Virchow, four (12%) were *S. enterica* Bredeney, and the rest belonged to other serotypes.

Most NTS bacteraemia cases (89%) received antibiotics that likely cover *Salmonella* species. Penicillins and third-generation cephalosporins were given to 50% and 47% of the cases, respectively. Antibiotic resistance was recorded for ampicillin (17%) and chloramphenicol (5%) (Supplementary material, Tables 2 and 3).

Discussion

Correlates of NTS bacteraemia were examined in comparison to salmonellosis and bacteraemia due to other pathogens. This approach was employed to decipher correlates of bacteraemia in NTS infections, and NTS infection in patients prone to bacteraemia.

Most NTS bacteraemia cases involved young children and the elderly. This supports the bimodal age distribution found in developed countries (Ispahani and Slack, 2000; Vugia et al., 2004), including Israel (Weinberger et al., 2004; Zaidenstein et al., 2010; Shimoni et al., 1999).

The correlates of NTS bacteraemia differed between children and adults. In line with a previous report (Shimoni et al., 1999), predisposing conditions for NTS bacteraemia in adults included various comorbidities and immunosuppression, while NTS

Table 2
Correlates of non-typhoidal *Salmonella* bacteraemia in patients aged ≤18 years.

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-Value[a]
Control group: salmonellosis patients			
Age (continuous variable)	0.93 (0.86–1.02)	0.99 (0.88–1.10)	0.8
Emergency room visit in the past 2 weeks (yes vs. no)	15.37 (6.00–39.35)	16.08 (5.77–44.86)	<0.001
Haemoglobin, g/dl (continuous variable)	0.77 (0.62–0.95)	0.88 (0.69–1.13)	0.3
Control group: patients with bacteraemia due to other pathogens			
Age (continuous variable)	0.98 (0.89–1.00)	0.98 (0.87–1.11)	0.8
Emergency room visit in the past 2 weeks (yes vs. no)	17.21 (5.98–49.51)	17.57 (5.36–57.57)	<0.001
Current surgery/invasive procedure (yes vs. no)	0.25 (0.09–0.73)	0.13 (0.03–0.59)	0.008
Antibiotic therapy in the past week	2.90 (1.08–7.82)	1.69 (0.50–5.75)	0.3

CI, confidence interval; OR, odds ratio.
[a] The p-value was obtained from the multivariable logistic regression model. Control group – salmonellosis patients: Nagelkerke R square = 0.39, Hosmer and Lemeshow test, $p=0.49$. Control group – patients with bacteraemia due to other pathogens: Nagelkerke R square = 0.43, Hosmer and Lemeshow test, $p=0.3$.

Table 3
Comparison of clinical characteristics between the study groups in patients aged >18 years.[a]

	NTS bacteraemia $n=49$	Salmonellosis $n=30$	Other bacteraemia $n=36$	p-Value 1	p-Value 2
Hospitalization in the past 2 weeks	6 (13%)	3 (10%)	5 (14%)	0.7	0.9
Antibiotic therapy in the past week	9 (21%)	2 (7%)	4 (11%)	0.10	0.3
Cancer	8 (16%)	1 (3%)	9 (25%)	0.14	0.3
Heart disease	27 (55%)	11 (37%)	18 (50%)	0.11	0.6
Atrial fibrillation	14 (29%)	1 (3%)	5 (14%)	0.007[b]	0.10
Congestive heart failure	11 (22%)	2 (7%)	7 (19%)	0.11	0.7
Chronic lung disease	6 (12%)	3 (10%)	4 (14%)	1.0	1.0
Hypertension	17 (35%)	8 (27%)	16 (44%)	0.4	0.3
Diabetes	13 (27%)	6 (20%)	12 (33%)	0.4	0.8
Renal failure	17 (35%)	6 (20%)	8 (22%)	0.16	0.2
Functional status – dependent	14 (33%)	4 (13%)	5 (14%)	0.06	0.05[b]
Charlson comorbidity score, mean (SD)	5.7 (3.5)	3.6 (2.8)	5.8 (3.1)	0.004[b]	0.9
Steroid therapy	10 (20%)	3 (10%)	2 (6%)	0.3	0.05[b]
Chemotherapy	3 (6%)	0 (0%)	5 (14%)	0.2	0.2
Current surgery/invasive procedure	10 (20%)	4 (13%)	10 (28%)	0.4	0.4
Mean haemoglobin (SD), g/dl	11.9 (2.6)	13.7 (2.4)	12.1 (2.6)	0.011[b]	0.9

NTS, non-typhoidal *Salmonella*; SD, standard deviation.
[a] p-Value 1 for the comparison between NTS bacteraemia cases and patients with salmonellosis; p-value 2 for the comparison between NTS bacteraemia cases and patients with bacteraemia due to other pathogens. The p-value was obtained by Chi-square test or Fisher's exact test, as appropriate, with the exception of haemoglobin levels, for which the Student t-test was used, and the Charlson comorbidity index, for which the Mann–Whitney test was used. Only one patient aged >18 years visited the emergency room prior to hospitalization. Information was missing on haemoglobin level for eight patients with NTS bacteraemia and three patients with bacteraemia due to other pathogens.
[b] After correction for multiple comparisons, $p > 0.05$.

Table 4
Correlates of non-typhoidal *Salmonella* bacteraemia in patients aged >18 years.

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-Value[a]
Control group: salmonellosis patients – model 1			
Age (continuous variable)	1.02 (0.99–1.05)	0.98 (0.94–1.02)	0.2
Atrial fibrillation (yes vs. no)	11.60 (1.43–93.56)	9.34 (0.90–97.12)	0.061
Haemoglobin, g/dl (continuous variable)	0.75 (0.59–0.93)	0.72 (0.54–0.95)	0.018
Charlson comorbidity score (discrete variable)	1.22 (1.05–1.43)	1.29 (1.00–1.66)	0.046
Control group: salmonellosis patients – model 2			
Age (continuous variable)		1.00 (0.97–1.03)	0.8
Atrial fibrillation (yes vs. no)		14.26 (1.35–150.68)	0.027
Haemoglobin, g/dl (continuous variable)		0.74 (0.57–0.96)	0.025
Cancer (yes vs. no)	5.66 (0.67–47.74)	7.54 (0.84–67.17)	0.07
Control group: patients with bacteraemia due to other pathogens			
Age (continuous variable)	1.00 (0.97–1.02)	0.98 (0.96–1.02)	0.2
Atrial fibrillation (yes vs. no)	2.48 (0.80–7.67)	3.34 (0.95–11.74)	0.06
Steroid therapy (yes vs. no)	4.35 (0.89–21.29)	5.22 (1.01–26.93)	0.048

CI, confidence interval; OR, odds ratio.
[a] The p-Value was obtained from the multivariable model. Control group – salmonellosis patients, model 1: Nagelkerke R square = 0.33, Hosmer and Lemeshow test, $p = 0.9$; model 2: Nagelkerke R square = 0.33, Hosmer and Lemeshow test, $p = 0.6$. Control group – patients with bacteraemia due to other pathogens: Nagelkerke R square = 0.13, Hosmer and Lemeshow test, $p = 0.16$.

bacteraemia typically occurred in otherwise healthy children (Yagupsky et al., 2002; Zaidi et al., 1999).

In children, an emergency room visit approximately 2 weeks prior to hospitalization was positively associated with NTS bacteraemia. *Salmonella* species do not typically cause nosocomial infections; therefore, it is assumed that NTS bacteraemia was present when the child visited the emergency room. The diagnosis may have been missed due to the non-specific clinical presentation of NTS bacteraemia (Shimoni et al., 1999; Yagupsky et al., 2002; Zaidi et al., 1999). Some observations support this assumption. First, many of the prior emergency room visits were labelled as viral infection or gastroenteritis. Second, some cases were contacted to recommend admission following a positive blood culture result. The study finding regarding the association between emergency room visit and NTS bacteraemia is consistent with a previous report from the USA (Zaidi et al., 1999). While blood culture may yield results in only 48 h and its sensitivity might be affected by antibiotic use, PCR assays for NTS provide more rapid diagnosis of the disease, which supports the inclusion of such assays in the clinical setting.

In this study, the percentage of case children who had invasive procedures/surgery during their hospitalization was lower than the percentage of control children with bacteraemia due to other pathogens (Table 2). This might imply that the development of bacteraemia due to other pathogens was facilitated by medical interventions and/or that the invasive procedures/surgery served as a port of entry.

In adults, compared to patients with salmonellosis, a high comorbidity burden was positively associated with NTS bacteraemia, with a 29% increase in the likelihood for each point increase in CCS. Another analysis that included the variable cancer instead of CCS showed a seven-fold increased likelihood of NTS bacteraemia in patients with cancer vs. those without cancer, but this association was not significant. Compared to patients with bacteraemia due to other pathogens, steroid therapy was positively associated with NTS bacteraemia. Both cancer and steroid therapy

are immunosuppressing conditions and can lead to a compromised host response. While it is known that various immunocompromising conditions such as cancer, HIV infection, systemic lupus erythematosus (SLE), and steroid therapy are major risk factors for NTS bacteraemia (Shimoni et al., 1999; Hsu et al., 2003; Hsu, 2005; Fisker et al., 2003), evidence regarding the role of other chronic illnesses (not immunosuppressing) is scarce and inconsistent. A previous study from Israel compared patients with NTS bacteraemia to patients with other Gram-negative bacteraemia and showed a positive association with immunosuppression, but not with ischemic heart disease, diabetes mellitus, or stroke (Shimoni et al., 1999). Similarly, a study from Taiwan showed that compared to patients with salmonellosis, NTS bacteraemia cases were more often immunodeficient (Hsu et al., 2003; Hsu, 2005), but no significant associations were found with diabetes, hypertension, coronary artery disease, or stroke (Hsu, 2005). Conversely, a study from Denmark showed that, regardless of age and immunosuppression, the risk of invasive NTS disease (mostly bacteraemia) was increased in relation to chronic diseases (e.g., ischemic heart disease and chronic obstructive pulmonary disease) (Fisker et al., 2003). These findings support the present study observations. The correlates of NTS bacteraemia identified in this study, and reports from developed countries, differ from those found in Sub-Saharan Africa, where HIV, young age, malaria, anaemia, and malnutrition are the main risk factors (Uche et al., 2017).

Interestingly, a positive association was found between chronic/paroxysmal atrial fibrillation and NTS bacteraemia when compared to salmonellosis patients and when compared to patients with bacteraemia due to other pathogens. Atrial fibrillation was not assessed in previous studies on risk factors for NTS bacteraemia (Shimoni et al., 1999; Hsu et al., 2003; Hsu, 2005; Fisker et al., 2003). Case reports on patients with NTS pericarditis or myocarditis have shown that these patients often suffer from atrial fibrillation and other arrhythmias (Ortiz et al., 2014; Hibbert et al., 2010). In the present study, none of the cases had endocarditis/pericarditis or myocarditis. It could be that NTS species increased heart rate and led to an exacerbation of pre-existing atrial fibrillation in these patients, but it could also be a marker of unmeasured factors. In the study data, atrial fibrillation was weakly related to age and congestive heart failure, but not to immunosuppression conditions such as cancer and steroid therapy (Supplementary material, Table S4).

While exact mechanisms of the associations between comorbidity burden and NTS bacteraemia need to be determined, the study observations have clinical and public health implications. From a clinical perspective, NTS bacteraemia should be suspected in cases of hospitalized febrile adults with comorbid conditions. From a public health perspective, future NTS vaccines under development for populations in Sub-Saharan Africa should also target adults with a high comorbidity burden in addition to immunocompromised patients.

This study demonstrates the importance of haemoglobin level as a significant correlate for NTS bacteraemia in adults. Each increase in haemoglobin level by 1 g/dl was associated with a 28% lower likelihood of having NTS bacteraemia. Haemoglobin level might be a marker of nutritional status, a proxy for acute bacteraemia in NTS infection, or both.

This study has limitations. Cases in the study likely represent those with severe disease, requiring hospitalization. However, most patients with bacteraemia will likely present with significant clinical symptoms. Additionally, medical and laboratory records were used, and testing was likely driven by clinical judgement (not necessarily documented). Two types of control group were included: one comprised hospitalized patients with bacteraemia due to pathogens other than NTS and the other control group consisted of patients hospitalized due to salmonellosis. We cannot guarantee that the control groups perfectly represent the population at risk. Data on the study variables were collected from the medical records. Obtaining and recording medical history might differ between physicians; however, there is no reason to suspect that physicians obtained the information selectively according to the patients' case or control status. To ensure maximum accuracy, data on the study variables were cross-validated using different sources: medical records, laboratory records, and nursing files. Prior antibiotic use might have limited the growth of *Salmonella* from blood; however prior antibiotic use was evident in both cases and controls.

Strengths of this study include the comprehensive assessment of correlates for NTS bacteraemia, data collected from both children and adults, a lengthy study period, and the utilization of two control groups from the same hospital, thus ensuring to some degree that cases and controls originated from the same source population served by the study centre.

In summary, in a high-income country, the correlates of NTS bacteraemia were found to differ between children and adults. In children, an emergency room visit 2 weeks prior to hospitalization was strongly associated with an increased likelihood of NTS bacteraemia, possibly reflecting a missed diagnosis and/or lack of improvement/worsening of illness. In adults, a high comorbidity burden and being immunocompromised increased the risk of bacteraemia in patients with *Salmonella* infection, while haemoglobin level might be protective. While steroid therapy might indicate immunosuppression, atrial fibrillation might be a marker of unmeasured factors.

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Ethical approval

The study protocol was approved by the Helsinki Committee of the Shaare Zedek Medical Centre.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2019.01.028.

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