A Population-Based Study on the Incidence, Risk Factors, and Outcome of Salmonella Bloodstream Infections in South Sweden 2012–2022

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ORIGINAL RESEARCH

A Population-Based Study on the Incidence, Risk Factors, and Outcome of *Salmonella* Bloodstream Infections in South Sweden 2012–2022

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ABSTRACT

Introduction: Invasive infections caused by *Salmonella* are a significant global health concern. This population-based study aimed to comprehensively analyze invasive *Salmonella* infections in South Sweden, focusing on incidence, clinical presentation, risk factors, and outcomes.

Methods: This population-based observational cohort study, conducted from 2012 to 2022, included all patients with *Salmonella* bloodstream infections (BSI) in the Skåne region, South Sweden. A control group consisted of patients with positive stool cultures/PCR for *Salmonella* but without BSI. Data were collected following a predefined study protocol from medical records. Standardized statistical analyses assessed patient characteristics, clinical presentation, and outcomes.

Results: Between 2012 and 2022, 149 patients with SBSI were identified, with the majority having non-typhoidal *Salmonella* (NTS) infections (95%). A declining trend in the incidence of SBSI was observed, with the highest incidence in 2012 (1.5 per 100,000 person-years) and the lowest in 2020 (0.3 per 100,000 person-years). Patients with BSI were more likely to be older, have comorbidities, be immunosuppressed, and use proton pump inhibitors (PPIs). Additionally, patients with BSI presented with fewer gastrointestinal symptoms, had a higher respiratory rate, lower saturation, and higher SOFA scores, suggesting a more septic presentation. Patients with SBSI had significantly longer hospital stays and higher 30-day, 90-day, 180-day, and 365-day mortality rates compared to the control group.

Conclusion: Invasive *Salmonella* infections are rare in South Sweden. In a cohort of enteric and invasive *Salmonella* infection, the absence of classic gastroenteritis symptoms increases the risk of *Salmonella* bloodstream infection. This study highlights the importance of distinguishing between clinical presentations to guide appropriate treatment when *Salmonella* infection is suspected. The declining trend in

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incidence, particularly associated with international travel, necessitates further investigation to understand contributing factors.

Keywords: Bacteremia; Antimicrobial resistance; Public health; One health; Foodborne pathogens

Key Summary Points

Why carry out this study?

We wanted to investigate the burden of *Salmonella* bloodstream infections (SBSI) in our setting, and to aid clinical management of patients with invasive *Salmonella* infections.

There is a general need for population-based studies investigating the incidence and temporal trend of SBSI, including both children and adults.

What did the study ask?

Are there differences in clinical presentation between patients with enteric and invasive *Salmonella* infection?

What was learned from the study?

In a cohort of enteric and invasive *Salmonella* infection, the absence of classic gastroenteritis symptoms increases the risk of SBSI.

What were the study outcomes/conclusions?

The mean age- and sex-standardized incidence of SBSI during the study period was 1.0 (0.8–1.2) per 100,000 person years, and the incidence saw a slight decrease during the study period, with a noteworthy decrease during the COVID-19 pandemic in 2020.

What has been learned from the study?

This study highlights the importance of distinguishing between clinical presentations to guide appropriate treatment when *Salmonella* infection is suspected.

INTRODUCTION

Gastrointestinal infections are a major cause of morbidity and mortality worldwide. It has been estimated that infections due to *Salmonella* cause over 90 million cases of diarrheal diseases each year, of which 85% are foodborne. In the USA, infection due to non-typhoidal *Salmonella* is the leading cause of hospitalization and death from gastrointestinal infections [1].

In the past, profound dehydration and fluid loss were the main cause of death from diarrhea. However, septic bacterial infections now account for an increasing proportion of diarrheal deaths [2]. To date, more than 2500 serotypes of *Salmonella* have been identified [2]. The *Salmonella* nomenclature is complex and somewhat inconsistent, separating the *Salmonella* genus into species, subspecies, subgenera, groups, subgroups, and serotypes (serovars). The *Salmonella* genus is commonly divided into two species: *Salmonella bongori* and *Salmonella enterica*, with *S. bongori* corresponding to subspecies V and *S. enterica* corresponding to subspecies I, II, IIIa, IIIb, IV, and VI. In humans and warm-blooded animals, 99% of *Salmonella* infections are caused by *S. enterica* subspecies I [3].

Three different types of salmonella infections occur in humans: non-invasive and non-typhoidal, invasive and non-typhoidal, and typhoidal enteric fever [3]. Out of all patients with *Salmonella* infection, 5–10% develop bloodstream infection (BSI), which can lead to localized infections such as meningitis, endocarditis, arthritis, and osteitis [3]. The *Salmonella* serotype appears to be a risk factor for the development of BSI, with infection with *Salmonella* Panama being the most important risk factor for *Salmonella* bacteremia in children under 16 years of age [4].

In areas of low-endemicity, international travel appears to be another risk factor associated with *Salmonella* BSI (SBSI), and destinations such as sub-Saharan Africa, the Middle East, and South-East Asia are high-risk regions for contracting invasive disease [5]. Other studies have found that increasing age and male sex are significant risk factors for non-typhoidal SBSI,

Table 1 Clinical features of patients with *Salmonella* BSI and non-BSI salmonellosis

Baseline characteristic, *n* (%)	**BSI *n* = 149**	**Non-BSI *n* = 299**	***p* value**
Age, median (range), years	61 (0–96)	48 (0–97)	< 0.0001
Female sex	63 (42%)	147 (49%)	0.17
Charlson Comorbidity index	3 (0–13)	1 (0–11)	< 0.0001
Myocardial infarction	21 (14%)	16 (5%)	0.0014
Congestive heart failure	11 (7%)	7 (2%)	0.01
Peripheral vascular disease	10 (7%)	7 (2%)	0.0216
Cerebral vascular accident or transient ischemic attack	12 (8%)	8 (3%)	0.0089
Dementia	5 (3%)	1 (0.3%)	0.0167
Connective tissue disease	14 (9%)	11 (4%)	0.0123
Diabetes mellitus	34 (23%)	26 (9%)	< 0.0001
Hemiplegia	4 (3%)	0 (0%)	0.0117
Solid tumor	13 (9%)	15 (5%)	0.12
Localized	6 (4%)	14 (5%)	0.76
Metastatic	7 (5%)	1 (0.3%)	0.0023
Leukemia	3 (2%)	4 (1%)	0.69
Lymphoma	3 (2%)	1 (0.3%)	0.11
Immunosuppression	31 (21%)	37 (12%)	0.0176
PPI treatment	54 (36%)	78 (26%)	0.0233
Site of acquisition			
Community	117 (79%)	271 (91%)	0.0004
Nosocomial	6 (4%)	1 (0.3%)	0.0064
Healthcare-associated	26 (17%)	27 (9%)	0.0093
Travel abroad within 14 days	61 (52%)	136 (59%)	0.21
Presentation of symptoms			
Duration of symptoms, median (range), days	4 (0–24)	3 (0.5–35)	0.0369
Diarrhea	95 (67%)	282 (95%)	< 0.0001
Bloody stool	11 (10%)	48 (24%)	0.0040
Abdominal pain	63 (55%)	176 (80%)	< 0.0001
Vomiting	58 (49%)	125 (53%)	0.45
Fever	104 (83%)	223 (87%)	0.30
Shaking chills	55 (83%)	93 (86%)	0.62
SOFA score 0–1	44 (30%)	94 (31%)	0.68

Table 1 continued

Baseline characteristic, *n* (%)	BSI*n* = 149	Non-BSI*n* = 299	*p* value
SOFA score ≥ 2	53 (36%)	54 (18%)	< 0.0001
Colitis/ileitis	9 (26%)	42 (69%)	< 0.0001
Cholecystitis	7 (21%)	0 (0%)	0.0005
Laboratory results			
Leukocyte counts × 10^9/L, median (range)	9.2 (2–31.1)	8.3 (0.3–44)	0.0256
Neutrophil counts × 10^9/L, median (range)	6.3 (0.5–29.4)	5.6 (0.5–19.2)	0.26
C-reactive protein mg/L, median (range)	111 (0.9–542)	95 (1.1–517)	0.23

Categorical variables are presented as No. and percentages based on the data available for each variable. Continuous variables are presented as median (range)
Chi-squared test is used for categorical data, Fisher exact test if sample size < 5
BSI bloodstream infection, *AIDS* acquired immunodeficiency syndrome, *PPI* proton pump inhibitors

while typhoidal SBSI was associated with younger age and no excess risk among male individuals [6]. However, risk factors for BSI are poorly defined, and there are not many previous studies investigating if the clinical presentation of SBSI and non-BSI differ. It is important to identify the patient with SBSI, in need of empirical antimicrobial treatment to avoid morbidity and mortality. In contrast, patients with non-invasive and non-typhoidal *Salmonella* infection are not treated with antibiotics.

The purpose of this study is to improve the knowledge about SBSI, focusing on clinical presentation, incidence, treatment, mortality, and putative risk factors. The primary aim was to investigate if patient characteristics differ between patients presenting with SBSI compared to patients with non-BSI *Salmonella* infection in our setting. Secondary aims included describing the incidence, trends, and outcomes of SBSI.

METHODS

Study Design and Study Population

This was a population-based observational cohort study including all patients with SBSI between 2012 and 2022 in Skåne, South Sweden. Patients were identified from the Department of Clinical Microbiology, Skåne University Hospital, Lund. Patients of all ages with SBSI were included in the study, regardless of the result of stool culture. Also, we included a control group of all patients identified from the Department of Clinical Microbiology, Skåne University Hospital, Lund, during the study period with a positive stool culture/PCR for *Salmonella* spp. without SBSI, as determined by negative blood cultures. The control group thereby comprised patients of all ages throughout the study, meeting the inclusion criterion of a positive stool sample for *Salmonella* spp. and concurrently testing negative for blood cultures to exclude invasive disease. The clinical laboratory serves the whole region of 1.4 million inhabitants, covering all private and public inpatient and outpatient clinics, from primary healthcare centers to the tertiary referral centers at the university hospital in Lund and Malmö. For the control patients, only the first fecal culture/PCR of *Salmonella* per patient per year was included. Patients could be included in the SBSI and control group multiple times during the study period, if the episodes were at least 2 months apart during separate medical care events. The group of patients with SBSI were further subgrouped into *Salmonella*

enterica subsp. *enterica* serovar Typhi (*S.* Typhi), *Salmonella enterica* subsp. *enterica* serovar Paratyphi (*S.* Paratyphi) A, B, or C, or non-typhoidal *Salmonella* (NTS). All medical records were reviewed according to a predefined study protocol and clinical data, including the patient's age and sex, presence of any immunodeficiency or chronic disease, vital signs, symptoms, laboratory results, antibiotic treatment, hospital admission and mortality, were recorded.

Variables

The following variables were retrieved: age, sex, Charlson comorbidity score, immunosuppression, active or history of cancer of the bowel, proton pump inhibitor (PPI) treatment, inflammatory bowel disease, previous or current substance abuse (including narcotics and alcohol), presence of *Salmonella* in blood culture (including number of blood cultures obtained, *Salmonella* serotype, polymicrobial growth, history of previous *Salmonella* bacteremia), antimicrobial resistance, presence of *Salmonella* in feces (including test method, *Salmonella* serotype, polymicrobial growth, history of gastroenteritis caused by *Salmonella*), presence of *Salmonella* in other sterile location, duration of symptoms, symptoms (diarrhea, bloody stools, abdominal pain, vomiting, fever, shivering chills), emergency department (ED) vital signs (systolic blood pressure, pulse, respiratory rate, saturation, body temperature, RLS), NEWS score [7], sepsis or septic shock at the ED or within 48 h of ED admission, laboratory results (including leukocyte and neutrophil counts, C-reactive protein, alanine aminotransferase tests, and lactate level), abdominal radiology (including computed tomography (CT) and ultrasound), site of acquisition (community, nosocomial, or healthcare-associated), international travel within 14 days prior to blood culture (including country or continent), admission to inpatient hospital care (including dates and duration), admission to the intensive care unit (including dates and duration), mortality (in hospital, 30 days, 90 days, 180 days, 365 days) and time to death (days) from obtained positive blood culture, antibiotics prior to blood culture, and empiric antibiotic therapy (including dates, duration, and *Salmonella* treatment indication).

Site of acquisition was defined as either community-acquired, nosocomial, or healthcare-associated according to the scheme of BSI published by Friedman et al. in 2002 [8]. The presence of certain symptoms, e.g., diarrhea, bloody stools, abdominal pain, vomiting, fever, and shivering chills, was documented if they were present in the patient's history or at the ED, but not if they occurred later in the hospital visit related to the *Salmonella* infection. Diarrhea was defined as the passage of three or more loose stools per day. Fever was defined as a body temperature > 38 °C. Sepsis and septic shock were defined according to the Sepsis 3 criteria [9]. Immunosuppression was defined as previous organ transplantation, prednisolone treatment > 15 mg per day or equivalent corticosteroid treatment, previous stem cell transplantation, primary immune defect, ongoing or recently terminated cancer treatment such as chemotherapy, dialysis or severe chronic kidney disease, or ongoing treatment for autoimmune disease. Antibiotics prior to blood culture include both ongoing and completed antibiotic treatment for *Salmonella* infection (e.g., if the patient received antibiotic treatment in another country or was prescribed by their primary care health center) or any other medical condition within 14 days prior to blood culture. For empiric antibiotics, only the first antibiotic preparation was documented. Treatment indication *Salmonella* was defined as a deliberate choice of antibiotics to treat a *Salmonella* infection.

Microbiology

The blood culture system used was BacT/Alert 3D (bioMérieux) until December 2012, and Bactec FX (Becton Dickinson) after that. Until February 2020 bacterial pathogens in fecal samples were detected using a primary culture-based method, with a PCR-directed culture method using the Amplidiag (Mobidiag Ltd) being used to identify *Salmonella* in fecal

samples after this point. Culture was done using Rappaport broth *Salmonella* CHROMAgar (CHROMAgar), and xylose-lysine-deoxycholate (XLD) agar. *S. enterica* isolates were confirmed using matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS: Bruker Daltonics, using the Bruker MBT Compass library) and underwent serotyping by slide agglutination with antisera (SSI Diagnostica and Reagensia). Serovars were determined following the White-Kauffmann-Le Minor scheme. Inconclusive cases were sent to the Public Health Agency of Sweden for whole-genome sequencing. Antimicrobial susceptibility testing (AST) was performed using either disk diffusion or gradient tests. Interpretation of the AST results was based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.

Statistics

Normally distributed continuous variables were reported as mean with standard deviation (SD), while non-normally distributed continuous variables were reported as median with range. Categorical data were reported as No. (%). The Student *t* test was used for normally distributed continuous data and the Mann–Whitney *U* test was used for non-normally distributed continuous data. The chi-squared test was used for categorical data, and the Fisher exact test was used when the sample size was < 5. A p value < 0.05 was considered statistically significant. For the comparative analysis between SBSI and non-BSI cases, patients under the age of 18 were excluded from the statistical analysis of the following variables (because of different reference values compared to adults): systolic blood pressure, respiratory rate, pulse, and total NEWS score. The annual incidences of SBSI were age- and sex-standardized to the 2022 Region Skåne standard population and reported as rates per 100,000 person-years with 95% confidence interval (CI). Risk factor analysis was conducted through a two-step process. Initially, a univariate analysis was employed to screen for potential factors associated with SBSI. Variables showing significant associations in the univariate analysis were then included in the subsequent multivariate analysis. The multivariate analysis utilized logistic regression models to identify independent risk factors for SBSI. Statistical analysis was performed using GraphPad Prism version 9.5.1 and R statistical Software, version 3, (R Foundation for Statistical Computing (https://www.r-project.org/).

Ethics

Ethical approval was obtained from the Swedish Ethical Review Authority (Dnr 2021-04866), and the study was conducted in accordance with the principles outlined in the Helsinki Declaration. As a result of the observational nature of the study, the need for patient consent was waived.

RESULTS

Patient and Microbiological Characteristics of Patients with BSI

Between 2012 and 2022, 149 patients with 149 episodes of SBSI were identified and included in the study. The median age of patients with BSI was 61 years (range 0–96), and 42% ($n = 63$) were women (Table 1). The most common age group for contracting SBSI was 61–70 years (Fig. 1). The median Charlson comorbidity index (CCI) was 3 (range 0–13), and 21% ($n = 31$) were immunosuppressed. Out of all patients with SBSI, 75% ($n = 112$) were simultaneously sampled for *Salmonella* in feces, of which 55% ($n = 82$) were positive.

Out of the 149 patients with SBSI, 142 (95%) were non-typhoidal *Salmonella* (NTS) and 7 (5%) were typhoidal *Salmonella* (TS). The most common serotype among SBSI was *Salmonella* Enteritidis (29%), followed by *S.* Typhimurium (15%) (Fig. 2). One of the patients with BSI was diagnosed with two different strains of *Salmonella* serotypes, *Salmonella* Dublin and *S.* Enteritidis, resulting in a total number of invasive *Salmonella* strains of 150. Furthermore, 5% ($n = 7$) were typhoidal *Salmonella* (*S.* Typhi, $n = 3$; *S.* Paratyphi A, $n = 3$; and Paratyphi B,

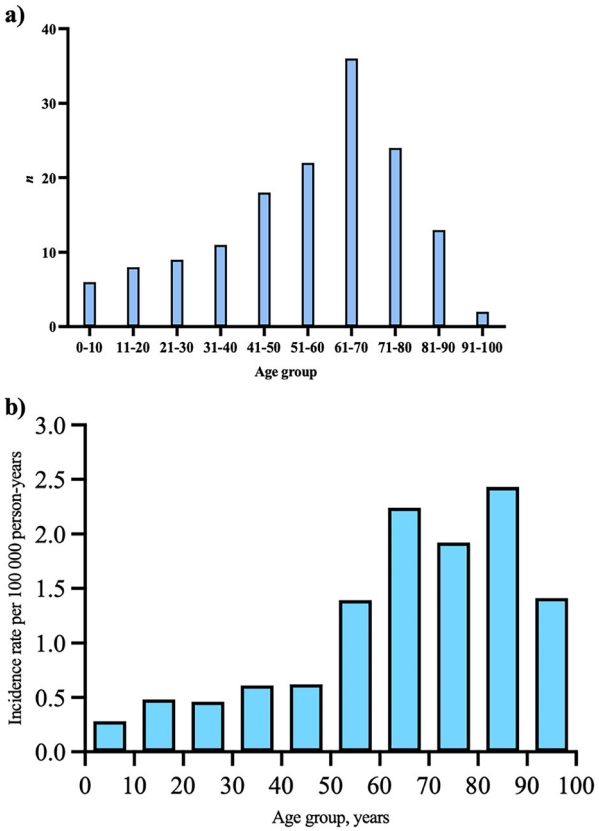

Fig. 1 **a** Patients with *Salmonella* bloodstream infections 2012–2022 by age group. **b** Incidence during the study period in relation to age groups

n = 1). None of the included patients had any recurrent SBSI. Overall, the rate of antimicrobial resistance for invasive *Salmonella* strains was low, and the highest rate of resistance was seen for ciprofloxacin (17%, Table A1).

Incidence and Trends of SBSI

The mean age- and sex-standardized incidence of SBSI during the study period was 1.0 (0.8–1.2) per 100,000 person-years. The incidence of SBSI saw a decrease during the period, with the highest incidence of 1.5 per 100,000 person-years in 2012, and the lowest incidence of 0.3 per 100,000 person-years in 2020 during the COVID-19 pandemic (Fig. 3).

Extraintestinal Manifestations of SBSI

In total, 19% (*n* = 29) of all SBSI had extraintestinal manifestations: 6% (*n* = 9) were positive for *Salmonella* in urine and 4% (*n* = 6) had *Salmonella* in a skin/wound culture. Simultaneous multiple extraintestinal manifestations were found in 5% (*n* = 8) of the patients. In four patients, *Salmonella* was found in urine simultaneously with either *Salmonella* growth in cerebrospinal fluid, in a skin/wound culture, in the auditory canal, or from the tip of a central dialysis catheter (CDC). Two patients were diagnosed with spondylodiscitis. One patient was diagnosed with both myocarditis and an iliopsoas abscess, with growth of *Salmonella*. In addition, one patient had *Salmonella* growth in the synovial fluid and surgical wound following knee replacement surgery. Simultaneous erysipelas infection occurred in three patients with SBSI. Furthermore, individual cases of *Salmonella* growth from the bile, from rectal secretions, and from the tip of a central dialysis catheter were found.

Non-BSI Control Group

In total, 299 patients had a positive stool culture/PCR for *Salmonella* spp. and a concurrent negative blood culture during the study period (Fig. 4). There were no *S.* Typhi or *S.* Paratyphi A, B, or C in the control group; all cases had a non-typhoidal *Salmonella* diagnosed. The median age of the control group was 48 years (IQR 0–97), and 49% (*n* = 147) were women. The median Charlson comorbidity index was 1 (IQR 0–11), and 12% (*n* = 37) were immunosuppressed. Baseline characteristics of SBSI and non-BSI cases patients are presented in detail in Table 1.

Characteristics of Patients with and Without SBSI

Patients with SBSI were older ($p < 0.0001$) compared to patients with enteritis, with a median age of 61 years (IQR 0–96) compared to 48 years (IQR 0–97). In addition, patients with SBSI had more comorbidities compared to

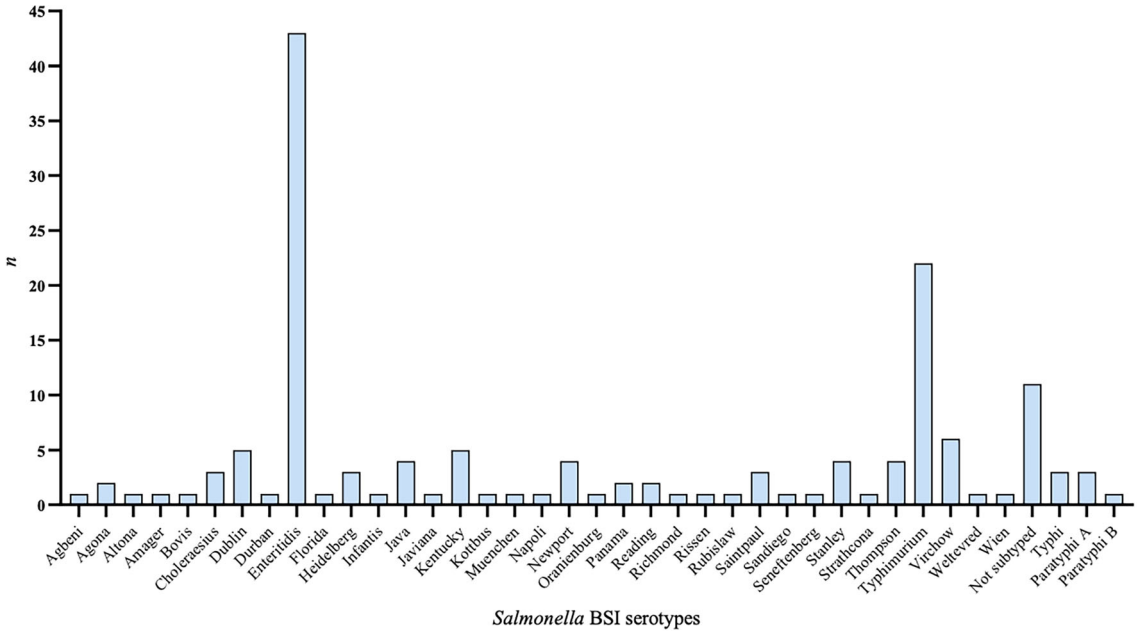

Fig. 2 *Salmonella* bloodstream infection (BSI) serotypes

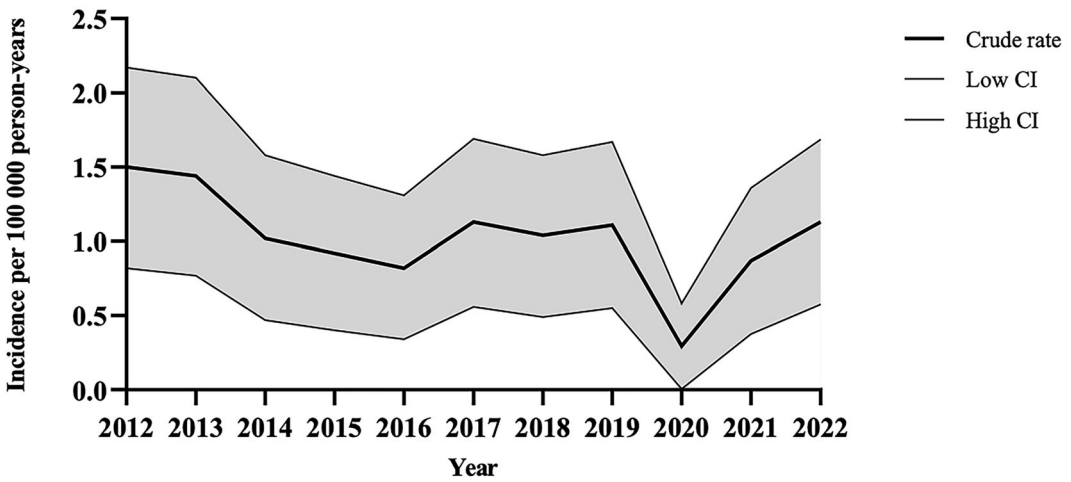

Fig. 3 Incidence of *Salmonella* bloodstream infection 2012–2022

controls, such as myocardial infarction (14% vs 5%, $p = 0.0014$), congestive heart failure (7% vs 2%, $p = 0.01$), peripheral vascular disease (7% vs 2%, $p = 0.0216$), cerebral vascular accident or transient ischemic attack (8% vs 3%, $p = 0.0089$), dementia (3% vs 0.3%, $p = 0.0167$), connective tissue disease (9% vs 4%, $p = 0.0123$), diabetes mellitus (23% vs 9%, $p < 0.0001$), hemiplegia (3% vs 0%, $p = 0.0117$), and metastatic solid tumor (5% vs 0.3%, $p = 0.0023$). As a result, the total Charlson comorbidity index of 3 (IQR 0–13) was significantly higher in the cases (CCI of controls 1 point, range 0–11, $p < 0.0001$). Furthermore, a

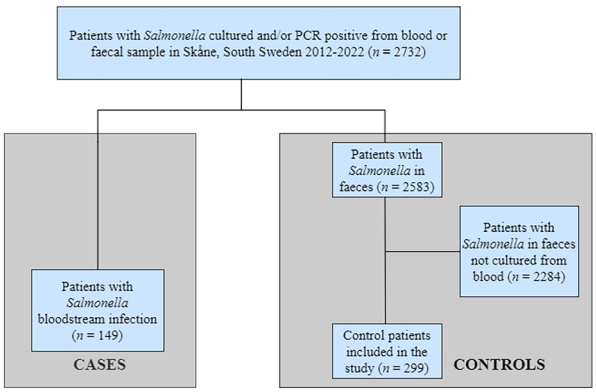

Fig. 4 Flowchart of inclusion and exclusion. Control patients were positive for *Salmonella* in faces and a negative blood culture

significant higher proportion of the cases were immunosuppressed (21%, $p = 0.02$) compared to the control group (12%). There was also a significantly higher proportion of cases receiving PPI treatment (36% vs 26%, $p = 0.02$) compared to the control group (Table 1).

A history of gastrointestinal symptoms such as diarrhea, bloody stools, and abdominal pain was significantly more common in controls (95% vs 67% $p < 0.0001$, 24% vs 10% $p = 0.0040$, and 80% vs 55% $p < 0.0001$, respectively). At presentation, patients with BSI had a significantly higher respiratory rate (21 vs 19, $p = 0.0004$) and a significantly lower saturation (97 vs 96, $p < 0.0001$). In addition, a significantly higher proportion of the patients with BSI had a RLS score of 2 (3% vs 0.7%, $p = 0.0440$) compared to the control group. Consequently, the patients with BSI had a significantly higher mean total NEWS score (4 vs 3, $p = 0.0006$) compared to the control group, and a higher proportion of the patients with SBSI had a total SOFA score ≥ 2 (36% vs 18, $p < 0.0001$) compared to the control group. There were no significant differences in body temperature, pulse, or systolic blood pressure between patients with SBSI and patients with enteritis.

Regarding laboratory results, the patients with SBSI had significantly higher leukocyte counts, alanine transaminase, and lactate levels ($p = 0.0256$, $p = 0.0009$, $p = 0.0016$, respectively). A significant higher proportion of the patients with BSI underwent abdominal CT during the hospital stay (32% vs 23%, $p = 0.046$) compared to the control group. However, there was no significant difference in the total number of pathological radiological findings between the groups (Table 1). In both patients with SBSI and patients with enteritis, colitis/ileitis was the most common radiological finding (respectively $n = 9$, 26% and $n = 42$, 69%). Additional findings in patients with BSI included cholecystolithiasis ($n = 4$, 12%), cholangitis ($n = 1$, 3%), aortitis ($n = 1$, 3%), infective native aortic aneurysm ($n = 1$, 3%), aortic graft/stent graft infection ($n = 1$, 3%), pyelonephritis ($n = 1$, 3%), anal abscess ($n = 1$, 3%), and miscellaneous ($n = 8$, 24% including appendiceal dilatation, signs of mesenteric inflammation, ileus, ascites, signs of pancreatic obstruction and atrophy).

The most common site of acquisition was community-acquired in both patients with BSI and patients without BSI (79% and 91%, respectively). However, in comparison, a significantly lower proportion of the patients with SBSI were community-acquired compared to the control group ($p = 0.0004$). Meanwhile, a significantly higher proportion of patients with SBSI were nosocomial (4%, $p = 0.0064$) or healthcare-associated (17%, $p = 0.0093$) compared to the control group (0.3%, 9%) (Table 1).

There was no significant difference in international travel between the groups; the majority of SBSI and controls had a history of international travel within 14 days prior to the *Salmonella* diagnosis. Among patients with BSI with a travel history, the most common destination was Southeast Asia (34%), sub-Saharan Africa (19%), Europe (17%), and Western Asia (13%) (Fig. 5).

The study identified a trend of decreasing numbers of travel-associated *Salmonella* infection cases during the study period, along with a declining annual proportion of cases linked to travel (Fig. 6).

Risk Factors for SBSI

In the multivariate analysis including all patients with SBSI, which included both adults and children, significant associations were observed between the incidence of the disease and certain factors. Notably, PPI use (OR 0.2, 95% CI 0.04–0.6, $p = 0.004$), the presence of diarrhea (OR 0.07, 95% CI 0.02–0.3, $p \leq 0.0001$), and a SOFA score of ≥ 2 (OR 3.2, 95% CI 1.1–9.1, $p = 0.03$) were identified as significant risk factors (Table 2).

However, when including adults ($n = 138$), only the presence of diarrhea (OR 0.08, 95% CI 0.03–0.3, $p \leq 0.0001$) was found to be statistically significant. Factors such as PPI use and SOFA score did not exhibit significant associations with invasive *Salmonella* infection in adults (Table 3).

Outcomes of Patients with SBSI and Patients Without BSI

Patients with SBSI were significantly more likely to be admitted to hospital and the intensive care unit (ICU) than patients without BSI (87% vs 78%, $p = 0.0344$ and 4% vs 0.3%, $p = 0.0064$, respectively) (Table 4). They also had significantly longer hospital and ICU stays (6 vs 3 days, $p < 0.0001$, 2 vs 1 days, $p = 0.0030$, respectively). There was no significant difference regarding in-hospital mortality between the patients with BSI and patients without BSI. However, for 30-day, 90-day, 180-day, and 365-day mortality, the patients with BSI had a significantly higher mortality (4% vs 1%, $p = 0.0429$; 7% vs 0.7%, $p = 0.0004$; and 9% vs 1%, $p < 0.0001$; 13% vs 2%, $p < 0.0001$, respectively) compared to the control group. For all patients who died during the hospitalization due to SBSI ($n = 4$), treatment was set to palliative care and antibiotic treatment was discontinued. A significantly higher proportion of the patients with SBSI received empiric antibiotic treatment (53% vs 36%, $p = 0.0008$).

Clinical Features of Typhoidal SBSI

In total, seven episodes of typhoidal SBSI were found during the study period (Table 5). The median age was 18, the median CCI score was 0, and the overall mortality rate was zero.

DISCUSSION

This study aimed to investigate the incidence, risk factors, and outcome of SBSI in South Sweden. The mean age- and sex-standardized incidence of SBSI during the study period was 1.0 (0.8–1.2) per 100,000 person years, and the incidence saw a slight decrease during the study period, with a noteworthy decrease during the COVID-19 pandemic in 2020. As around half of the SBSI cases in our study were travel-related, international travel likely influence the incidence of SBSI in Sweden. In our study, a declining trend was noted in the annual proportion of *Salmonella* infections associated with travel. However, the limited number of travel-related cases in our study prevents a robust assessment of the significance of this trend, and it should be noted that information on international travel was missing for more than one-fifth of the SBSI cases. Nonetheless, the diminishing trend observed in travel-related cases warrants further research investigating the epidemiological factors of *Salmonella* infections in the context of global travel patterns such as travel destination, specific serotypes associated with travel-related cases, and travel behavior.

In Sweden, infection with *Salmonella* is a notifiable disease, and data from the Public Health Agency of Sweden reveal a declining trend in the number of annual cases during the study period, including both BSI and enteric cases (https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden). This further supports that the preventive work to reduce *Salmonella*-contaminated food by the Swedish Food Agency is successful.

A study from Denmark in 2006 found a higher mean incidence of 2.3 per 100,000 person-years, and the incidence steadily increased during the study period [10]. This could be explained by the fact that Denmark has a

	Region	Non-typhoidal *Salmonella*, *n* (%)	Typhoidal *Salmonella*, *n* (%)	Total, *n* (%)
1	South America	3 (5%)	0 (0%)	3 (5%)
2	Europe	11 (18%)	0 (0%)	11 (17%)
3	North Africa	4 (7%)	0 (0%)	4 (6%)
4	Sub-Saharan Africa	11 (18%)	1 (25%)	12 (19%)
5	Western Asia	8 (13%)	0 (0%)	8 (13%)
6	North Asia	1 (2%)	0 (0%)	1 (2%)
7	South Asia	3 (75%)	0 (0%)	3 (5%)
8	South-East Asia	22 (37%)	0 (0%)	22 (34%)

Fig. 5 *Salmonella* bloodstream infection from different regions. South America (cases from countries Brazil, Chile). Europe (cases from countries Albania, Denmark, France, Greece, Italy, Poland, Spain), North Africa (cases from countries Egypt, Morocco). Sub-Saharan Africa (cases from countries Uganda (TS), Ghana, Kenya, Ethiopia, Gambia, Senegal, Seychelles, Tanzania). Western Asia (cases from countries Turkey, Lebanon). North Asia (cases from Russia). South Asia (cases from countries Nepal and Pakistan). Southeast Asia (cases from countries Thailand, Vietnam, Philippines, Malaysia, Indonesia, Myanmar). *TS* typhoidal *Salmonella*, *NTS* non-typhoidal *Salmonella*

higher *Salmonella* incidence in general than Sweden [11].

Notably, these trends align with findings from several other studies, including research in the Netherlands (2012), a long-term study in Queensland, Australia (2007–2016), and a multinational population-based study spanning Australia, Finland, Canada, and Denmark (2000–2006), all of which reported increasing incidence rates [6, 12, 13]. Given the substantial regional variation in the incidence of *Salmonella* bacteremia, there is a compelling need for further research to comprehensively explore contributing factors. These may encompass travel behaviors, food practices, agricultural influences, and other pertinent variables, aligning with a One Health approach. We are not aware of any *Salmonella* outbreaks in our region during the study period. Overall, the incidence of SBSI

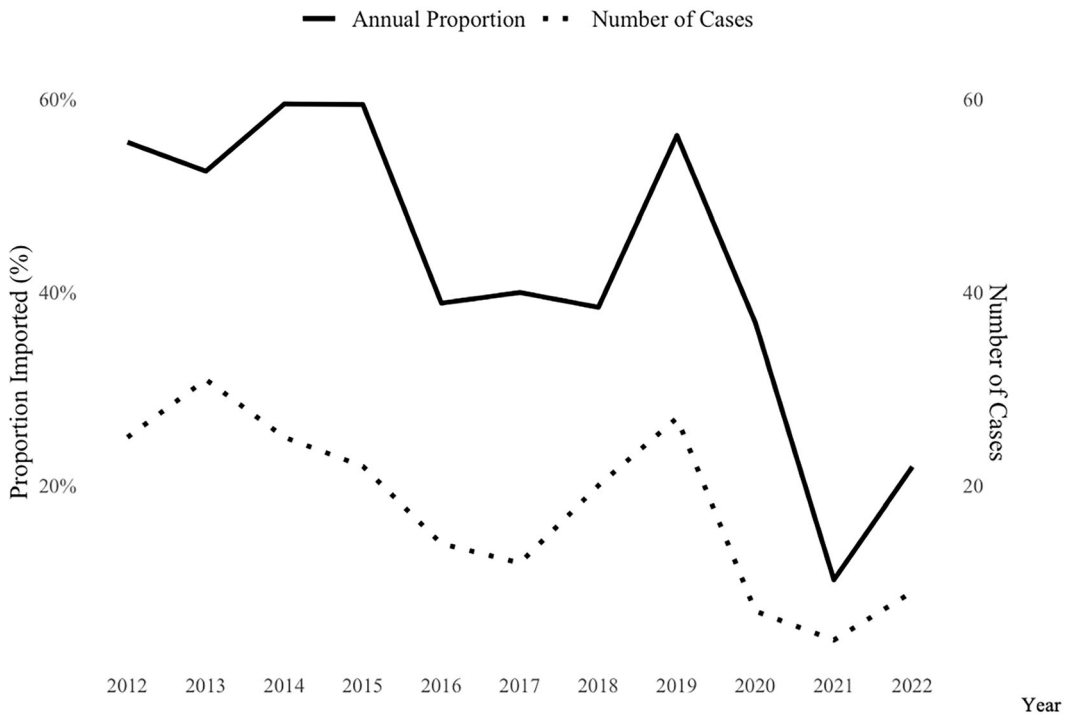

Fig. 6 Proportion and total number of *Salmonella* cases associated with travel annually, 2012–2022

in this study confirms that SBSI is a rare medical condition in our setting [3, 14].

The *Salmonella* strains included in this study exhibited low antimicrobial resistance towards antibiotics commonly used in healthcare. The highest rate of resistance was found for ciprofloxacin (17%), which is lower than what has been reported for the first-line antibiotic therapy with tetracycline, ampicillin, ceftriaxone, and ciprofloxacin from the USA (20%) and England (34%) [15, 16]. Higher rates of antimicrobial resistance have been reported from countries in South Asia, sub-Saharan Africa, and East Asia where *Salmonella* is endemic and antimicrobial resistance is a major concern [17, 18]. It should be noted that 1% of the strains included in our study were resistant to cefotaxime, which constitutes the first-line antibiotic for treating sepsis and suspected BSI in Sweden [19].

The 30- and 180-day mortality rates in this study were 3% and 9%, respectively, which are lower than those found in a 2006 study from Denmark, where the 30-day and 180-day mortality were 11% and 22%, respectively [10]. Studies in neighboring Denmark reported more cases of domestic *Salmonella* cases, which tend to have a worse prognosis compared to imported cases [5, 20, 21]. In our study the mortality rates, as well as the need for and duration of both hospitalization and intensive care, were significantly higher in patients with SBSI than in patients without BSI. This is not surprising but supports the fact that SBSI is a serious medical condition with substantial impact [22–25].

Patients with SBSI in this study exhibited a distinctive clinical presentation when compared to patients without BSI. Notably, they presented with fewer gastrointestinal symptoms, aligning with previous findings by Yen et al. [26], who concluded that the majority of adults with SBSI do not display symptoms of gastroenteritis. Furthermore, our observations

Table 2 Multivariate analysis including all BSI episodes

	BSI $n = 149$	Non-BSI $n = 255$	OR (95% CI)	*p* value	AOR (95% CI)	*p* value
Age, years						
0–39	34	106	Ref		Ref	
40–61	43	77	1.8 (1.1–3.1)	0.03	1.8 (0.5–6.5)	0.3
≥ 62	72	72	4.0 (2.3–6.7)	≤ 0.0001	0.8 (0.04–15.8)	0.9
CCI						
0	70	187	Ref		Ref	
1	24	28	2.3 (1.2–4.2)	0.008	5.0 (0.4–68.0)	0.2
≥ 2	55	40	3.7 (2.2–6.0)	≤ 0.0001	7.8 (0.3–194.1)	0.2
Immunosuppression						
No	118	227	Ref		Ref	
Yes	31	28	2.1 (1.2–3.7)	0.008	0.5 (0.1–1.8)	0.3
PPI						
No	95	189	Ref		Ref	
Yes	54	66	1.6 (1.1–2.5)	0.03	0.2 (0.04–0.6)	0.004
Diarrhea						
No	47	12	Ref		Ref	
Yes	95	242	0.1 (0.05–0.2)	≤ 0.0001	0.07 (0.02–0.3)	≤ 0.0001
Bloody stool						
No	94	136	Ref		Ref	
Yes	11	41	0.4 (0.2–0.8)	0.009	1.5 (0.3–6.9)	0.6
Abdominal pain						
No	51	36	Ref		Ref	
Yes	63	157	0.3 (0.2–0.5)	≤ 0.0001	0.3 (0.1–1.1)	0.06
SOFA score ≥ 2						
No	44	82	Ref		Ref	
Yes	53	47	2.1 (1.2–3.6)	0.007	3.2 (1.1–9.1)	0.03

BSI bloodstream infection, *PPI* proton pump inhibitors, *CCI* Charlson Comorbidity Index, *SOFA* Sequential Organ Failure Assessment

indicated a statistically longer duration of symptoms (such as abdominal pain) and diarrhea among patients with BSI when compared to the control group. This finding corresponds with the research conducted by Bar-Meir et al. [27], who noted that children with SBSI experienced a more extended duration of symptoms in comparison to those with *Salmonella*

Table 3 Multivariate analysis including all BSI episodes in adults

	BSI $n = 138$	Non-BSI $n = 212$	OR (95% CI)	*p* value	AOR (95% CI)	*p* value
Age, years						
18–49	31	86	Ref		Ref	
50–66	43	69	1.7 (1.0–3.1)	0.06	0.9 (0.4–2.4)	0.9
≥ 67	64	57	3.1 (1.8–5.4)	≤ 0.0001	0.6 (0.1–4.0)	0.6
CCI						
0	59	146	Ref		Ref	
1–2	41	47	2.2 (1.3–3.6)	0.004	2.1 (0.5–10.0)	0.3
≥ 3	38	19	4.9 (2.6–9.3)	≤ 0.0001	2.8 (0.4–19.3)	0.3
Immunosuppression						
No	31	26	Ref		Ref	
Yes	107	186	2.1 (1.2–3.7)	0.01	0.6 (0.2–1.7)	0.3
PPI						
No	54	65	Ref			
Yes	84	147	1.5 (0.9–2.3)	0.1		
Diarrhea						
No	86	203	Ref		Ref	
Yes	45	8	0.08 (0.03–0.2)	≤ 0.0001	0.08 (0.03–0.3)	≤ 0.0001
Bloody stool						
No	11	26	Ref			
Yes	86	118	0.6 (0.3–1.2)	0.2		
Abdominal pain						
No	57	136	Ref			
Yes	49	36	0.3 (0.2–0.5)	≤ 0.0001	0.9 (0.4–2.0)	0.8
SOFA score ≥ 2						
No	52	44	Ref			
Yes	42	75	2.1 (1.2–3.7)	0.008	2.1 1.0–4.5)	0.06

BSI bloodstream infection, *PPI* proton pump inhibitors, *CCI* Charlson Comorbidity Index, *SOFA* Sequential Organ Failure Assessment

gastroenteritis. It is worth noting, however, that the difference in the duration of symptoms and diarrhea, although statistically significant, may not be considered clinically significant, as it amounted to just one additional day. Additionally, the duration of symptoms remains highly contingent on when the patient seeks medical care and, consequently, when blood

Table 4 Outcome of patients with *Salmonella* bloodstream infection and non-BSI *Salmonella*

	BSI ***n*** **= 149**	**Non-BSI** ***n*** **= 299**	***p*** **value**
Length of hospital stay median (range)	6 (1–70)	3 (1–80)	< 0.0001
Admitted to the intensive care unit	6 (4%)	1 (0.3%)	0.0064
Mortality			
30 days	4 (3%)	1 (0.3%)	0.0429
90 days	10 (7%)	2 (0.7%)	0.0004
180 days	13 (9%)	3 (1%)	< 0.0001
365 days	17 (13%)	5 (2%)	< 0.0001
Empiric antibiotics	78 (53%)	108 (36%)	0.0008

BSI bloodstream infection

cultures are obtained during the course of the disease.

Importantly, our study revealed a noteworthy clinical distinction between SBSI and non-BSI cases. We observed that the presence of diarrhea significantly decreases the risk of developing BSI. In practical terms, this suggests that patients presenting with diarrhea as their primary symptom may not necessarily require antibiotic treatment. Conversely, individuals with invasive *Salmonella* infections tend to present with a more severe clinical profile that includes signs of sepsis, underlining the importance of distinguishing between these clinical presentations to guide appropriate treatment decisions, when *Salmonella* infections are suspected and managed. While our study was conducted in a specific geographic area, the association between symptoms of gastroenteritis and decreased risk of BSI aligns with findings from other disparate epidemiological profiles, suggesting that these findings could be generalized to other settings [28].

This finding holds critical clinical importance when faced with management of suspected *Salmonella* infections. When considering whether to initiate antibiotic treatment, the presence of gastroenteritis symptoms may suggest refraining from treatment, especially in patients without other signs of severity.

Regarding PPI treatment, other studies have found an association between PPI treatment and non-typhoidal salmonellosis [29–33], as well as other causes of gastroenteritis [34]. To the best of our knowledge, however, there are no studies exploring the risk of SBSI and the use of PPIs. In our study, there was statistically significant less PPI treatment in the SBSI cohort compared to non-BSI cases, an association that

Table 5 Clinical features of patients with typhoidal *Salmonella* BSI

	Typhoidal ***Salmonella*** ***n*** **= 7**
Age, median (range), years	18 (7–46)
Female sex	2 (29%)
Charlson Comorbidity index	0
Symptoms	
Duration of symptoms, median (range), days	11 (4–24)
Diarrhea	5 (71%)
Bloody stool	0 (0%)
Abdominal pain	4 (100%)
Vomiting	2 (40%)
Fever	7 (100%)
Shaking chills	3 (100%)
SOFA score 0–1	3 (43%)
SOFA score ≥ 2	1 (14%)
Inpatient hospital care	4 (57%)
Days of hospital care, median (range)	6 (4–7)
Travel abroad within 14 days	4 (57%)
Overall mortality rate	0 (0%)

did not remain when only adults were analyzed. We are unable to explain this association, and more research is needed in this area to investigate this further.

In our study, we did not find that age was a risk factor for SBSI. Prior studies have found that higher age is a risk factor for invasive infection [6, 10, 12, 16, 35, 36]. Also, some studies have identified a higher risk of developing invasive infection in infants [25, 35, 37]. In contrast to many other studies, this study found no significant risk increase for male sex and SBSI [6, 12, 16, 25, 35].

Furthermore, patients with SBSI had significantly higher leukocyte counts and alanine transaminase and lactate levels. Although again the differences are small and may not be clinically relevant, the finding is consistent with previous published research [27, 38].

Both comorbidities and immunosuppression have previously been identified as plausible risk factors for SBSI in other studies [16, 22, 27, 39–41]. Although significant in the univariate analysis, we did not associate comorbidities and immunosuppression with SBSI.

International travel was common in both patients with SBSI and controls. We did not find that international travel was associated with an increased risk of SBSI, which contradicts the findings of the study by Koch et al. [5] in Denmark 2011. As the domestic cases of *Salmonella* are low in Sweden compared to many countries, international travel likely impacts both BSI and non-BSI *Salmonella* cases.

Risk factors such as age, sex, comorbidities, immunosuppression, and international travel have thus been identified as risk factors of SBSI in other studies, but not in ours. This could be due to the different populations studied, the use of different definitions of these variables, and the relatively few SBSI cases included in our study.

We refrained from investigating differences in risk factors and clinical presentation of typhoidal versus non-typhoidal *Salmonella* as the number of typhoidal SBSI cases was very low.

One of the strengths of this study is that it is population-based, including all BSI in the region, with data from one microbiological lab including all ten hospitals in Skåne, South Sweden. We standardized incidence rates to age and gender to enable comparisons with other populations. We did not select individuals for the control group but included all patients with *Salmonella* in feces with a concurrent negative blood culture, and the control group was twice as large as the group of cases. Moreover, there was no selection based on age, as the study included both children and adults. We did not exclude patients from the group of cases nor the control group. In Sweden, all individuals have a unique personal number which makes it easy to link information from medical records, laboratory results, and microbiological findings to each individual, which is another strength of this study. In addition, the study started in 2012, when MALDI-TOF was established in clinical routine use at the clinical microbiology laboratory, improving the differentiation between bacterial species.

Our study has some limitations. A major limitation is that overall, a substantial number of patients with *Salmonella* detected in their stool samples did not undergo blood culture during the study period. Out of the 2732 patients included with positive cultures/PCR from blood or stool only 448 (16%) were cultured from blood, potentially missing a vast number of SBSI. This limitation potentially underestimated the number of BSI cases included in the study and could hence impact our analyses of risk factors. It is plausible that younger, healthier individuals seeking primary care for gastroenteritis were less likely to undergo blood culture, potentially introducing bias into the risk factor analysis. Also, not every variable was available from the medical records for every individual in the study. For some variables, there were considerable missing data, which is a common limitation of retrospective studies. These variables included some symptoms that were not accounted for, not all blood tests were taken, and most notably there was no record of international travel in more than a fifth of SBSI cases. The substantial missing data in these areas may have implications for the comprehensiveness and accuracy of our analyses and findings. Another limitation is the

rather modest number of study participants, even if there were no patients excluded and we included all patients with at least one positive blood culture. In addition, 44% of the control group had received antibiotic treatment prior to blood culture, which could make their blood cultures false negative.

It is important to monitor the incidence, trends, and resistance patterns of SBSI, to provide a basis for recommendations for empirical antibiotics and to oversee preventive measures. To fully investigate the prevalence and burden of invasive *Salmonella* infection, more patients with suspected *Salmonella* need to be blood cultured.

CONCLUSION

Invasive *Salmonella* infections are rare in South Sweden. In a cohort of enteric and invasive *Salmonella* infection, the absence of classic gastroenteritis symptoms increases the risk of SBSI. This study highlights the importance of distinguishing between clinical presentations to guide appropriate treatment when *Salmonella* infection is suspected. The declining trend in incidence, particularly associated with international travel, necessitates further investigation to understand contributing factors.

Author Contributions. Oskar Ljungquist, Torgny Sunnerhagen, and Anna Blackberg conceived the study. Lina Bjorklund drafted the manuscript and created images, which Anna Blackberg and Torgny Sunnerhagen critically revised. Anna Blackberg performed the statistical analyses. All authors approved the final version of the manuscript.

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Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Lina Björklund, Ylva Mattisson, Anna Bläckberg, Torgny Sunnerhagen, and Oskar Ljungquist have no interests to disclose.

Ethical Approval. Ethical approval was obtained from the Swedish Ethical Review Authority (Dnr 2021-04866), and the study was conducted in accordance with the principles outlined in the Helsinki Declaration. As a result of the observational nature of the study, the need for patient consent was waived.

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