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Original article

Changing epidemiology of invasive non-typhoid *Salmonella* infection: a nationwide population-based registry study

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ABSTRACT

Objectives: Non-typhoid *Salmonella* (NTS) may invade beyond the intestine, causing bacteraemia, sepsis, and infection of normally sterile sites. The epidemiology of invasive NTS (iNTS) infection is under-researched. We determined trends, risk factors, serotype distribution, antimicrobial resistance (AMR), and attributable sources of iNTS infection in a high-income setting.

Methods: 22,837 records of culture-confirmed human salmonellosis cases and 10,008 serotyped *Salmonella* isolates from five putative animal reservoirs (pigs, cattle, broilers, layers, reptiles) in the Netherlands during 2005–2018 were retrieved from national surveillance registries. Risk factors for iNTS infection were identified using logistic regression analysis. Source attribution modelling was based on serotyping, prevalence, and exposure data.

Results: The average annual percentage of iNTS infections was 4.6% (range 3.5–5.7%). An increase in iNTS infections was observed since 2012 (odds ratio (OR) 1.09, 95% confidence interval (95% CI) 1.04–1.14). Increased iNTS infection risk was associated with wintertime (OR 1.37, 95% CI 1.12–1.66), male sex (OR 1.73, 95% CI 1.51–1.99), older age (ORs: 3.27 to 16.33, depending on age groups), and living in rural areas (OR 1.54, 95% CI 1.23–1.93). While 52% of iNTS infections (n = 950) were caused by serotypes Enteritidis and Typhimurium, those displaying the highest invasiveness relative to their occurrence were Dublin (32.9%, n = 163), Panama (21.6%, n = 106), and Poona (14.1%, n = 71). Cattle were a larger source of iNTS than non-iNTS infections (12.2% *vs*. 7.6%). Lower AMR and multi-resistance rates were observed among iNTS (37.9%) than non-iNTS isolates (48.6%).

Discussion: The increase in iNTS infections, which is reported also in other countries, is of public health and clinical concern. The underlying reasons seem to be multi-factorial in nature. iNTS infection risk depends more on the infecting serotypes and patient demographics, and less on the attributable reservoirs and AMR profiles. **L. Mughini-Gras, Clin Microbiol Infect 2020;26:941.e9–941.e14**

Introduction

Non-typhoid *Salmonella* (NTS) infection is the second most reported zoonosis in Europe [1]. In high-income countries, NTS usually causes self-limiting diarrhoeal illness with low case fatality [2]. However, NTS may sometimes invade beyond the intestine, causing bacteraemia, sepsis and infection of normally sterile sites (invasive NTS (iNTS) infection).

In The Netherlands (~17 million population), an estimated 27 000 symptomatic NTS infections occur annually [3], ~70% of which caused by serotypes Enteritidis and Typhimurium (including its monophasic variant 1,4,[5],12:i:-) [4]. Salmonellosis incidence has decreased since the mid-1990s in The Netherlands [4], with ~80% of infections being attributable to pigs and layers as reservoirs and a concurrent decrease in egg-associated salmonellosis and an

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increase in pig- and reptile-associated salmonellosis [4–7]. No data on iNTS infections have been reported, although these are important given the observed epidemiological changes.

In low-income settings [8], Typhimurium and Enteritidis are the primary serotypes associated with iNTS infections, which are most prevalent among HIV-infected individuals, infants, elderly people and young children with malaria, anaemia and malnutrition. An Australian study [9] reported increasing iNTS infection incidence, with high rates among males, infants, elderly people and infections with serotype Virchow.

To better understand iNTS epidemiology in high-income settings, we determined trends, risk factors, serotype distribution, antimicrobial resistance (AMR) and attributable sources of iNTS infection in The Netherlands.

Methods

Data

We used national surveillance data for 22 837 serotyped *Salmonella* isolates from 21 547 patients in The Netherlands from January 2005 to December 2018. This surveillance system has an estimated 62% population coverage and is based on a laboratory network submitting *Salmonella* isolates voluntarily to the National Institute for Public Health and the Environment (RIVM) for subtyping [4,10]. Available patient metadata are a unique identifier, sex, age, sampling date, residence location and specimen type (faeces, blood, urine, etc.). Socio-economic status (SES) and urbanization degree per residence postcode were obtained from Statistics Netherlands (www.cbs.nl). AMR profiling has been performed since 2008 on a random subsample (77–90%) of submitted isolates. The minimum inhibitory concentration (MIC) was used to classify each isolate as resistant/susceptible based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) epidemiological cut-offs (ECOFFs). For antibiotics with EUCAST-undefined ECOFFs, we used cut-offs of the Dutch National Antimicrobial Surveillance System (MARAN) [11].

For source attribution, we retrieved all serotyped *Salmonella* isolates from pigs ($n = 1153$), cattle ($n = 3317$), broilers ($n = 4226$), layers ($n = 1202$), and reptiles ($n = 110$) collected during 2005–2018 by the Dutch veterinary services (livestock) and private clinics (reptiles) during their diagnostic/surveillance activities on animals and foods. These isolates were also submitted to the RIVM and analysed like the human isolates.

Definitions

An NTS infection was defined as an individual resident in The Netherlands with a culture-confirmed *Salmonella* infection during 2005–2018. We used previous definitions [9]. Infections with serotypes Typhi and Paratyphi A/B/C were excluded, except Paratyphi B biovar Java, which predominantly causes enterocolitis. Infections with *Salmonella* isolated from blood, cerebrospinal fluid, peritoneal fluid, pleural fluid, synovial fluid, bone or other normally sterile sites were defined as iNTS infections. An individual could meet this definition more than once if subsequent iNTS infections with the same serotypes were reported >1 month apart. Infections with *Salmonella* isolated from faeces, urine, vomit, sputum, skin, soft tissue abscesses and wounds were defined as non-iNTS infections. An individual could meet this definition more than once if subsequent non-iNTS infections with the same serotypes were reported >6 months apart. NTS infections with the same serotypes in both normally sterile and non-sterile sites <1 month from one another were only considered iNTS infections.

Data analyses

Like Parisi et al. [9], invasiveness was defined as the proportion of iNTS infections to the total number of NTS infections. Invasiveness was calculated by serotype, patient demographics, year and season. Effects of age, sex, season, year, SES, urbanization degree and serotype (independent variables) on iNTS infection risk, as well as differences in AMR between iNTS and non-iNTS infections, were assessed using multivariable logistic regression models including the iNTS/non-iNTS status or the antimicrobial resistance/susceptible status of the isolates as binary dependent variable. Independent variables were predefined based on availability and clinical/epidemiological relevance; no variable selection procedure was applied as the number of covariates was small relative to the observations and no collinearity was present (variance inflation factor = 1.02). Associations were expressed as odds ratios (OR) and respective 95% confidence intervals (95% CI). A complete record analysis was performed. Inter-annual linear trends and seasonal differences were assessed including year (continuous variable) and season (categorical variable) in the models. A cluster-robust sandwich variance estimator was used to account for multiple infections in the same patients. All models showed overall statistical significance (likelihood-ratio test, $p < 0.05$) and goodness-of-fit (Hosmer–Lemeshow test, $p > 0.05$). Analyses were performed using Stata 15 (StataCorp, College Station, TX, USA). A $p < 0.05$ was considered statistically significant.

Source attribution

Source attribution was performed using the 'modified Dutch model' based on all serotyping data, as described previously [4–7]. Briefly, this model inferred probabilistically the sources of human infections by comparing the serotype distributions of patients and animal reservoirs, weighted by the NTS prevalence in each reservoir and human exposure thereto (Table S1). Travel- and outbreak-related infections and infections with serotypes undetected in sources were excluded. Attributions for the most common serotypes among iNTS infections were also presented. Differences in attributions between iNTS and non-iNTS infections were tested using a two-sample test of proportions with Bonferroni's correction.

Ethics

This study was performed on fully deidentified surveillance data, so no ethics approval was required.

Results

Descriptives

In total, 22 419 NTS infections (21 181 patients) were reported in 2005–2018; 605 (2.7%) were excluded because we had no specimen information and 888 (4.0%) because patients' age and/or sex were unknown. Of the remaining 20 926 NTS infections (19 876 patients), 952 (4.5%) were invasive (922 patients), but two were caused by the same serotypes in the same patients <1 month apart, giving 950 (4.5%) iNTS infections (921 patients). Of the 19 974 non-iNTS infections, 118 were caused by the same serotypes in the same patients <6 months apart, and five were caused by the same serotypes in patients with concomitant iNTS infections, giving 19 851 non-iNTS infections (19 162 patients).

Trends

The average annual number of iNTS infections was 68 (range 48–96), corresponding to an average annual proportion of iNTS infections (to the total number of NTS infections) of 4.6% (range 3.5–5.7%). Over the years, iNTS infections increased while non-iNTS infections decreased (Fig. 1). The overall inter-annual trend in iNTS infections was not significant (p 0.442). However, an inflection point was observed in 2012, with a significantly decreasing trend in iNTS infections from 2005 to 2012 (OR 0.93, 95% CI 0.90–0.97, p 0.000) and a significantly increasing trend afterwards (OR 1.09, 95% CI 1.04–1.14, p 0.000). The number of either iNTS or non-iNTS infections was highest in autumn and summer. However, invasiveness was highest in winter (5.6%) and lowest in autumn (4.1%), with significant differences between winter and summer (OR 1.37, 95% CI 1.12–1.66, p 0.002), winter and autumn (OR 1.42, 95% CI 1.17–1.72, p 0.000), and autumn and spring (OR 0.79, 95% CI 0.65–0.97, p 0.021).

Serotype distribution

The primary serotype concerning the number of iNTS infections was Enteritidis (28.2%), followed by Typhimurium (23.6%) and Dublin (8.9%) (Table S1). Focusing on serotypes with ≥10 iNTS infections, the highest invasiveness concerned Dublin (32.9%), Panama (21.6%) and Poona (14.1%). Besides these serotypes, those significantly associated with iNTS infection were Oranienburg, Chester, Heidelberg, Napoli, Virchow and Enteritidis. For Enteritidis and Typhimurium, invasiveness had similar temporal patterns as the number of iNTS infections, but this was different for Dublin, as its invasiveness decreased while the number of Dublin infections increased over time (Fig. S1).

Risk factors

Increased iNTS infection risk was associated with male sex (OR 1.73) and age, with all age groups >14 years having a significantly increased risk than children <5 years (OR 3.27–16.32), and living in rural areas (OR 1.54) (Table 1).

Antimicrobial resistance

Resistance to ampicillin, gentamicin, sulfamethoxazole and tetracycline was higher among non-iNTS infections, whereas resistance to florfenicol was higher among iNTS infections. iNTS infections were less likely to be multiresistant than non-iNTS infections (Table 2).

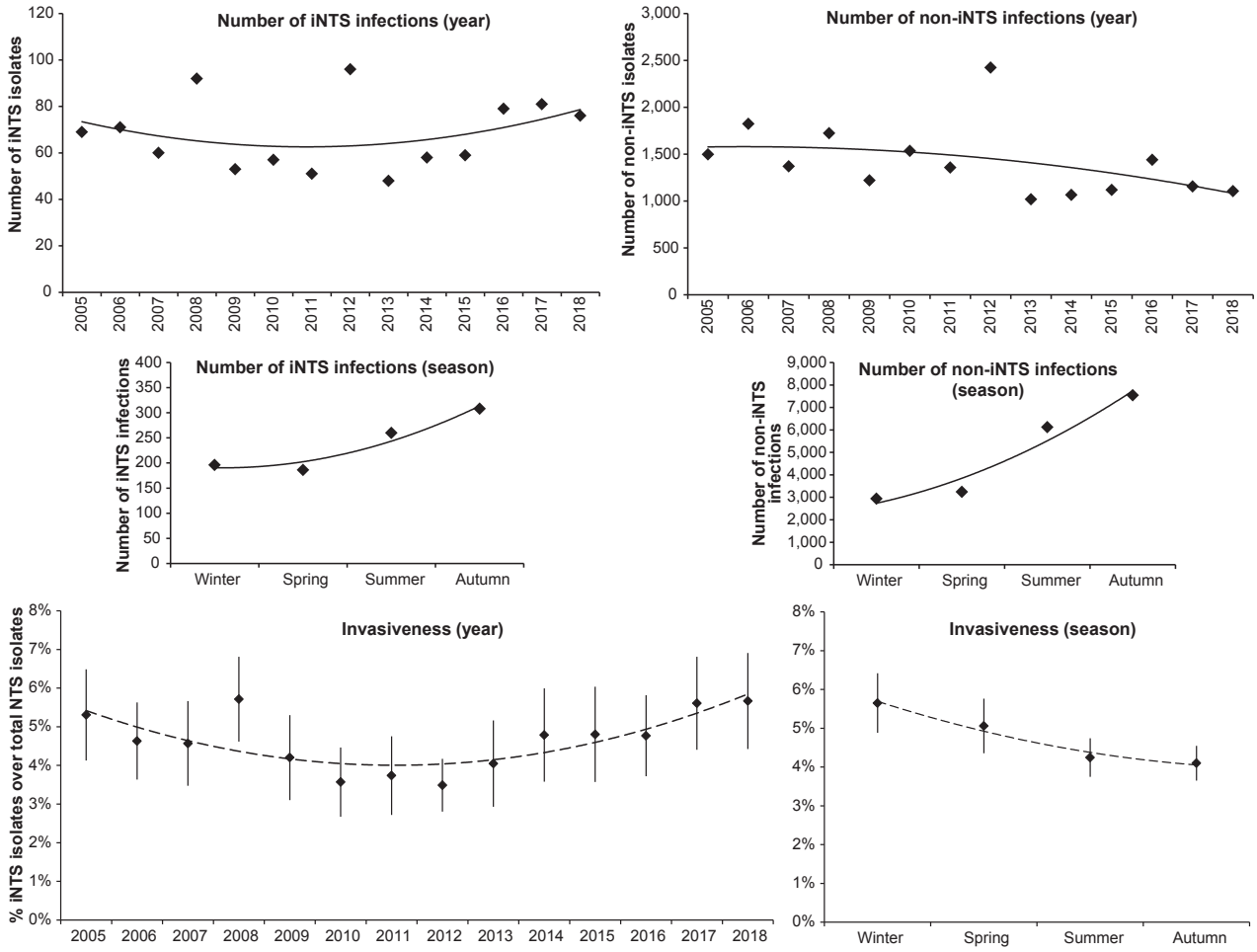

Fig. 1. Temporal patterns of the number of invasive and non-invasive non-typhoid *Salmonella* infections and their proportion (invasiveness), The Netherlands, 2005–2018. iNTS, invasive non-typhoid Salmonella; non-iNTS, non-invasive non-typhoid Salmonella. Estimates of invasiveness are adjusted for age, sex, socio-economic status, urbanization degree, and clustering of infections at the patient level (see Table 2 for categorization of these variables). Error bars denote 95% confidence intervals. A second order polynomial trendline is fitted to the data.

Table 1
Adjusted odds ratios for invasive non-typhoid *Salmonella* (iNTS) infection by sex, age, socio-economic status, and degree of urbanization, The Netherlands, 2005–2018

	No. NTS isolates	Invasiveness (95% CI)[a,b]	OR[a]	95% CI[a]		p[a]
Sex						
Female	10,941	3.5% (3.2–3.9%)	Reference			
Male	9860	5.8% (5.3–6.3%)	1.73	1.51	1.99	0.000
Age (years)						
0–4	2745	0.8% (0.5–1.2%)	Reference			
5–14	3386	1.0% (0.7–1.3%)	1.20	0.67	2.05	0.510
15–24	3397	2.7% (2.1–3.3%)	3.27	2.03	5.26	0.000
25–44	3668	3.4% (2.8–4.0%)	4.25	2.69	6.71	0.000
45–64	3655	6.5% (5.7–7.3%)	8.38	5.39	13.02	0.000
65–84	3385	11.2% (10.1–12.2%)	15.16	9.82	23.42	0.000
>85	565	11.9% (9.2–14.6%)	16.33	9.95	26.79	0.000
SES[c]						
High	6649	4.5% (3.9–5.1%)	Reference			
Intermediate	6648	4.7% (4.1–5.3%)	1.05	0.88	1.25	0.596
Low	6653	4.6% (4.0–5.1%)	1.02	0.86	1.21	0.834
Unknown	851	4.4% (0.0–11.4%)	0.97	0.16	6.02	0.975
Urbanization degree[d]						
Urban	4451	3.8% (3.2–4.3%)	Reference			
Intermediate	11,964	4.6% (4.2–5.1%)	1.25	1.05	1.50	0.014
Rural	3570	5.6% (4.7–6.5%)	1.54	1.23	1.93	0.000
Unknown	816	4.3% (0.0–11.4%)	0.75	0.12	4.86	0.764

OR, odds ratio; 95% CI, 95% confidence interval; NTS, non-typhoid *Salmonella*.
[a] Estimates are adjusted for year of isolation, season, and clustering of infections at the patient level in addition to the variables shown in the table.
[b] Proportion of invasive NTS infections to the total number of NTS infections in that stratum.
[c] SES, socio-economic status, classified as high, intermediate or low, based on a standard index including income, occupation and education per postal code area obtained from Statistics Netherlands (www.cbs.nl).
[d] Urban: >2500 addresses/km^2; intermediate: 500–2500 addresses/km^2; rural: <500 addresses/km^2 per postal code area, obtained from Statistics Netherlands (www.cbs.nl).

Source attribution

Of the 950 iNTS and 19 851 non-iNTS infections, 81 iNTS (8.5%) and 2419 non-iNTS (12.2%) infections were travel related, 161 iNTS (16.9%) and 4821 non-iNTS (24.3%) infections were outbreak related, and 45 iNTS (4.7%) and 836 non-iNTS (4.2%) infections were caused by serotypes undetected in the sources. Therefore, 663 iNTS and 11 775 non-iNTS infections were attributed: 36.2% of iNTS infections were attributed to layers, followed by pigs (33.8%), cattle (12.2%), reptiles (10.2%) and broilers (7.6%) (Fig. 2). These attributions did not differ significantly from non-iNTS infections, except for cattle, which was significantly higher ($p < 0.001$) among iNTS infections. Attributions showed differences in patients aged 0–4, 5–14 and 15–24 years, for which reptiles as sources of iNTS infection scored higher (32%, 31% and 24%, respectively) than for non-iNTS infection (10%, 6% and 12%, respectively; all $p < 0.001$) (Fig. S2). Attributions also differed according to the most common serotypes among iNTS infections: Panama, Typhimurium and 1,4,[5],12:i:- were mostly associated with pigs (77%, 70% and 71%, respectively), Enteritidis with layers (87%), Thompson with reptiles (69%) and Dublin with cattle (65%) (Fig. S2).

Discussion

We analysed 14 years of NTS surveillance data in The Netherlands and observed more iNTS infections since 2012. Wintertime, male sex, older age and rural areas were risk factors for iNTS infection. Approximately half of iNTS infections were caused by Enteritidis and Typhimurium, the most common serotypes. However, Dublin, Panama and Poona displayed the highest invasiveness relative to their occurrence. iNTS isolates were generally less (multi-)resistant than non-iNTS isolates. The attributable sources of iNTS and non-iNTS infections did not differ significantly, except for cattle, which was more important for iNTS infections.

Increasing iNTS infection incidence has also been reported in Australia [9]. The reasons for the increase we observed are unclear and could be multifactorial. The documented increase in reptile-associated salmonellosis [4] might contribute, as it often results in invasive disease and hospitalization [12]. There was a reversal of the pre-2012 decreasing trend in iNTS infections, with a peak in 2008 due to a Panama outbreak (highly invasive serotype) linked to fresh fruit juice [13] and another peak in 2012 due to a Thompson outbreak (lowly invasive serotype) linked to smoked salmon [14]. This reversal was driven by concurrent increases in Enteritidis and Typhimurium/1,4,[5],12:i:- invasiveness, whereas generally high numbers of Dublin infections drove the increase in iNTS infections with this serotype, as its invasiveness decreased over time. These trends suggest changes in the biology (e.g. dominant lineages) and/or epidemiology (e.g. exposure patterns) of these serotypes, possibly leading to increased virulence of circulating Enteritidis and Typhimurium/1,4,[5],12:i:- strains, and increased exposure to (less invasive) Dublin strains. Comparative genomics on iNTS and non-iNTS strains may shed lights on changed population genetics.

Enteritidis and Typhimurium as the most common serotypes among iNTS infections agree with findings from the United States [15,16] and Greece [17]. Dublin, Panama and Poona as the most invasive serotypes also concur with findings from Australia [9] and the United States [15,16]. Particularly Dublin, a cattle-adapted serotype typically causing bloodstream infections, often showed the highest invasiveness [9,15–19]. Yet, the Australian study reported Virchow as the most invasive serotype [9]. However, Virchow is uncommon in The Netherlands (~1%) and the United States [9]. Attributions reflected the serotype distribution, with cattle being more important for iNTS due to its strong association with Dublin.

As previously described [9,15,19], we found increased iNTS infection risk with advancing age, which is likely to be due to generally higher rates of comorbidities at older ages predisposing to invasive disease [20]. As the Dutch population (alike other high-income countries) is experiencing an ever-increasing life expectancy with a shift towards older ages, this vulnerable group will grow. Immunocompromised patients are also more prone to iNTS infection [21]. Although we had no information on immunocompetence, patients'

Table 2
Antibiotic resistance among invasive and non-invasive non-typhoid *Salmonella* infections, The Netherlands, 2008–2018

Antibiotics	Resistance among iNTS infections[a] ($n = 667$)	Resistance among non-iNTS infections[a] ($n = 12\,224$)	OR[a]	95% CI[a]		p[a]
Ampicillin	24.3% (20.9–27.5%)	30.5% (29.7–31.4%)	0.72	0.60	0.87	0.001
Azithromycin[c]	3.0% (1.3–4.7%)	3.5% (3.0–4.1%)	0.85	0.46	1.54	0.585
Chloramphenicols	14.1% (11.5–16.7%)	12.8% (12.2–13.4%)	1.11	0.89	1.39	0.340
Chloramphenicol	13.9% (11.3–16.5%)	12.8% (12.2–13.4%)	1.10	0.88	1.38	0.384
Florfenicol[b]	14.5% (10.9–18.2%)	9.8% (9.1–14.5%)	1.59	1.17	2.16	0.003
Fluoroquinolones	14.9% (12.1–17.7%)	14.7% (14.1–15.4%)	1.01	0.80	1.27	0.924
Ciprofloxacin	14.7% (11.9–17.4%)	14.2% (13.6–14.9%)	1.04	0.82	1.31	0.763
Nalidixic acid	14.5% (11.7–17.2%)	14.3% (13.7–14.9%)	1.01	0.80	1.28	0.919
Cephalosporins	1.7% (0.8–2.6%)	2.3% (2.0–2.5%)	0.74	0.42	1.28	0.278
Cefotaxime	1.6% (0.7–2.4%)	2.1% (1.9–2.4%)	0.73	0.41	1.29	0.276
Ceftazidime	0.5% (0.0–1.0%)	1.0% (0.8–1.2%)	0.51	0.20	1.30	0.160
Aminoglycosides	28.5% (25.4–31.7%)	29.9% (29.2–30.6%)	0.92	0.74	1.13	0.425
Gentamicin	1.9% (0.9–2.9%)	3.6% (3.3–4.0%)	0.52	0.31	0.88	0.014
Kanamycin[b]	1.5% (0.3–2.7%)	1.8% (1.5–2.1%)	0.81	0.35	1.89	0.627
Streptomycin[b]	48.8% (43.3–54.2%)	49.1% (47.9–50.2%)	0.99	0.79	1.24	0.921
Meropenem[c]	0.0% (0.0–0.0%)	0.0% (0.0–0.0%)	—	—	—	—
Sulfamethoxazole	25.0% (21.7–28.4%)	31.4% (30.6–32.2%)	0.72	0.60	0.87	0.001
Tetracycline	24.5% (21.1–27.8%)	32.1% (31.3–33.0%)	0.68	0.56	0.82	0.000
Tigecycline[c]	5.8% (3.3–8.3%)	7.7% (6.9–4.4%)	0.74	0.46	1.19	0.215
Trimethoprim	7.9% (5.9–10.0%)	9.0% (8.5–9.6%)	0.87	0.65	1.16	0.346
Multiresistance (class-level)[d]	Proportion of iNTS infections ($n = 327$)	Proportion of non-iNTS infections ($n = 5232$)	OR[a]	95%CI[a]		p[a]
0 class (no resistance)	62.1%	51.4%	Reference			
1 class ('mono-resistance')	14.1%	16.4%	0.76	0.54	1.07	0.116
2–3 classes	9.2%	18.2%	0.41	0.27	0.60	0.000
4–5 classes	11.3%	9.9%	0.89	0.61	1.31	0.567
≥6 classes	3.4%	4.2%	0.58	0.30	1.10	0.094

OR, odds ratio; 95% CI, 95% confidence interval; iNTS, invasive non-typhoid *Salmonella;* non-iNTS, non-invasive non-typhoid *Salmonella.*
[a] Estimates are adjusted for year of isolation, season, sex, age, socio-economic status, degree of urbanization and clustering of infections at the patient level in addition to the variables shown in the table.
[b] Available until 2013 ($n = 7327$).
[c] Available from 2011 ($n = 5564$).
[d] Based on 5559 isolates with complete information for all antibiotics.

age may mirror deteriorated immunity (immunosenescence), which would explain why iNTS infection risk increased with age. Male sex as risk factor for iNTS infection may be a consequence of sex-associated dietary choices and high-risk behaviours [9,15,16,19]. Moreover, sexual dimorphism in bacterial infections has been attributed to differential levels of sex hormones and genetic factors [22]. Differences in exposure, either food-related or environmental, may determine the increased iNTS infection risk in rural areas [9,15,19].

This study has limitations. As we used passive surveillance data, the true number of NTS infections is much higher and the infections included here represent the most severe ones. Moreover, iNTS infections are generally more severe than non-iNTS ones, so selective reporting bias cannot be excluded. However, we found an increase in the absolute number of iNTS isolates and their proportion to the total, indicating that more iNTS (and not just fewer non-iNTS) isolates are being reported since 2012 (but not before then), while there is no indication that laboratories changed their reporting policy. To ensure comparability with previous studies, we used similar case definitions [9]. Yet, these definitions were not comprehensive of all possible clinical outcomes. Specifically, the iNTS definition did not account for some complications (e.g. endocarditis) that might be missed during the index episode causing relapsing symptoms months after first manifestation. Moreover, some non-iNTS isolates from, for example soft-tissue abscesses might derive from haematogenous spread with negative blood cultures. While we could not differentiate precisely between new cases and long-term carriers, only 3.1% iNTS and 3.4% non-iNTS infections had more than one isolate reported, so any potential impact of misclassification was marginal. We did not have complete information on factors like travel, ethnicity, immunocompetence and comorbidities. However, we had data on SES, age and rurality, which are surrogate risk factors. While there have been no changes in surveillance during the study period, many laboratories introduced molecular screening methods for detecting positive samples to culture. However, because we only analysed isolate data, which are obtained from culture, our results were not affected. Finally, iNTS epidemiology might differ in other high-income countries.

Invasiveness was highest in winter. Most studies identified summer as the most at-risk season for iNTS infection due to increased travel abroad and lax food preparation (outdoor cooking) [9,19,23].

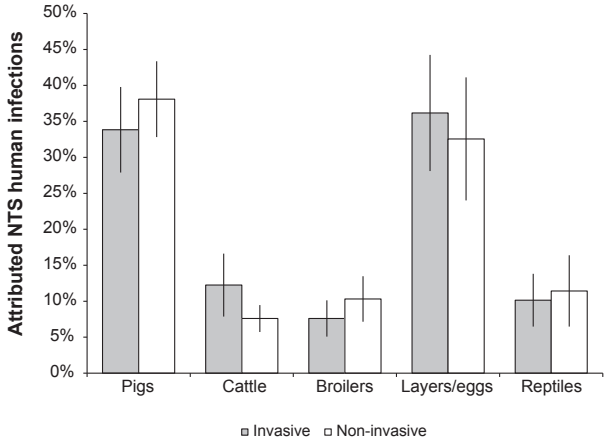

Fig. 2. Attributions of invasive and non-invasive non-typhoid *Salmonella* infections to animal sources, The Netherlands, 2005–2018. Error bars represent 95% confidence intervals.

However, a Danish study observed an NTS bacteraemia peak in December-January among people with comorbidities [23], speculating that comorbidities may be exacerbated by concomitant respiratory infections common in the coldest months. iNTS infections being generally less (multi-)resistant than non-iNTS infections are reassuring, as these often need antibiotic treatment. The reasons for this remain largely unclear and deserve more attention in future studies. The observed resistance mainly reflected the common ampicillin–chloramphenicol–sulfamethoxazole–tetracycline (ACSuT) penta-resistance profile in *Salmonella* genomic island 1 [11], and resistance to clinically important compounds like cephalosporins was less frequent.

In conclusion, we provided important insights into iNTS epidemiology in a high-income country. Increasing iNTS infections, differential serotype effects on invasiveness and higher iNTS infection rates among males, older people, rural areas and wintertime, as well as the attributable sources and therapeutic implications due to AMR, call for continuous (i)NTS surveillance. The drivers of the changing iNTS epidemiology require further investigations like genomic analyses of iNTS/non-iNTS isolates and exposure assessments for the highly invasive strains. Because NTS is a zoonotic agent mainly transmitted to humans from animals, food, or the environment, a One Health approach is needed to further improve our understanding of (i)NTS epidemiology.

Transparency declaration

All authors declare no competing interests. This study received no specific financial support and was therefore supported internally by the authors' institutions.

Author contributions

L.M.G., E.F., R.P. and J.D. conceived and designed the study. M.H., K.V. and B.W. generated the data. J.D. curated the data set. L.M.G. and R.P. analysed the data. L.M.G. wrote the first draft of the paper. All authors contributed to interpreting the results, drafting subsequent versions of the paper, critically reviewing and approving the final version as submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.11.015.

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