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## Severity of infection and seasonal variation of non-typhoid *Salmonella* occurrence in humans

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### SUMMARY

Non-typhoid *Salmonella* infections may present as severe gastroenteritis necessitating hospitalization and some patients become septic with bacteraemia. We hypothesized that the seasonal variation of non-typhoid *Salmonella* occurrence in humans diminishes with increased severity of infection. We examined the seasonal variation of non-typhoid *Salmonella* infections in three patient groups with differing severity of infection: outpatients treated for gastroenteritis ( $n = 1490$ ); in-patients treated for gastroenteritis ( $n = 492$ ); and in-patients treated for bacteraemia ( $n = 113$ ). The study was population-based and included all non-typhoid *Salmonella* patients in a Danish county from 1994 to 2003. A periodic regression model was used to compute the peak-to-trough ratio for the three patient groups. The peak-to-trough ratios were 4.3 [95% confidence interval (CI) 3.6–5.0] for outpatients with gastroenteritis, 3.2 (95% CI 2.4–4.2) for in-patients with gastroenteritis, and 1.6 (95% CI 1.0–2.8) for in-patients with bacteraemia. We conclude that the role of seasonal variation diminishes with increased severity of non-typhoid *Salmonella* infection.

### INTRODUCTION

Numerous surveillance studies of non-typhoid *Salmonella* (NTS) infections in developed countries have reported a distinct seasonal variation, with peaks and troughs occurring in the warmer and colder months respectively [1–7]. Higher incidence in warmer months has been explained by exogenous risk factors, e.g. travel abroad [8, 9], consumption of dishes containing raw eggs [10], or lax hygiene related to outdoor cooking [3]. With regard to patient characteristics seasonal NTS variation has been related mainly to

age and *Salmonella* serotypes [1–4, 7]. To our knowledge, few studies have compared seasonal variation among patients with infections of differing severity or between outpatients and in-patients. About 95% of NTS cases reported in surveillance studies occur as self-limiting gastroenteritis (GE) and most of the remaining 5% occur in bacteraemia patients [11].

In this study we examined the seasonal NTS variation in three patient groups, with differing severity of clinical NTS infection: GE outpatients, GE in-patients, and bacteraemia in-patients. We hypothesized that the seasonal variation, with peak incidence in the warmer months, would be less prominent for patient groups with more severe clinical NTS symptoms. The more severe symptoms may reflect a more susceptible host status.

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## METHODS

### Setting

During the 10-year study period (1994–2003), North Jutland County, Denmark, had an average population of 492 843 residents (Statistics Denmark: www.statistikbanken.dk). The Danish medical care system is tax-financed and free of charge for all residents. Initial medical contacts are with a general practitioner (GP), who may refer patient to one of the county's eight public hospitals.

### Microbiological procedures

All specimens from the county were submitted by a GP or a hospital ward. From 1994 to August 1997, all stool cultures were performed by Statens Seruminstitut (SSI), Copenhagen, Denmark. Starting in September 1997, they were performed by the Department of Clinical Microbiology (DCM), Aalborg Hospital, Aalborg, Denmark. Both laboratories used the same procedures for culturing *Salmonella*: 10 µl stool was suspended in 7.0 ml selenite broth (SB) (SSI Diagnostika, Hillerød, Denmark), which was plated on SSI enteric medium [12] and XLD agar (Oxoid, Basingstoke, Hants., UK), all were incubated for 18–24 h at 35 °C. Then, a second plating of SB on XLD agar (incubated for 18–24 h at 35 °C) was performed. Methods of identifying *Salmonella* were reported previously [12]. Blood cultures performed by the DCM used methods also described previously [13]. The Kaufmann–White scheme was used for typing of isolates (*Salmonella* Enteritidis and *S. Typhimurium* at the DCM, other serotypes at SSI).

### Data retrieval

All Danish residents have a unique 10-digit personal identification number, which permits linkage between most administrative registries.

SSI maintains a central database containing information on all *Salmonella*-positive specimens (www.mave-tarm.dk). The database includes patients' personal identification number (which incorporates age and gender), serotype, and date of receipt of specimen. For our analyses 1994–1997 data were retrieved from this database. For the 1998–2003 period we were able to retrieve the same information on GE patients from the laboratory information system maintained by the DCM (ADBakt, Autonik,

Sköldinge, Sweden). Unlike the SSI database, this database also includes specimen type. To identify cases of *Salmonella*-related bacteraemia, we used the North Jutland County Bacteraemia Database [15] to retrieve data on all *Salmonella*-positive blood specimens processed during the study period (1994–2003). Fifty-three NTS bacteraemia cases, which were registered both in the 1994–1997 SSI database and in the North Jutland County Bacteraemia Database, were deleted from the SSI dataset. All remaining cases in the SSI dataset were assumed to be GE patients. Because separate seasonal analyses of the 1994–1997 and 1998–2003 data showed only minor discrepancies, data from both periods were merged for further analyses.

### Data linkage

Since 1977, non-psychiatric hospital discharge diagnoses have been recorded in the County Hospital Discharge Registry of North Jutland, using the International Classification of Diseases (ICD) system (ICD-8 until 1994 and ICD-10 thereafter, as ICD-9 was never implemented in Denmark) [16]. To determine which GE patients were treated on an in-patient basis, laboratory data on GE patients were linked to this registry. This permitted identification of patients who had been hospitalized with an NTS-related diagnosis within  $\pm 1$  month of the receipt date of the first NTS-positive specimen. The main NTS-related diagnoses (NTS infection or diarrhoea due to presumed infectious cause) were retrieved by ICD-8 codes 003, 009 and ICD-10 codes A02, A09. In addition, ICD-8 codes 001, 002, 038.89, 0.38.99, 535 and ICD-10 codes A01, A41.5, A41.8, A41.9, K29 (typhoid fever, paratyphoid fever, septicaemia, gastritis) were included to detect possible misclassifications. For all patients comorbid diseases diagnosed in the 5-year period prior to the first NTS-positive specimen were also retrieved. We categorized comorbidity using the Charlson index [17], which includes 19 major disease categories and assigns points to each of these (with more points associated with the more severe disease categories).

### Statistical analysis

Except for bacteraemia, the analytical unit was an NTS episode, defined as beginning on the date that the first NTS-positive specimen was received by the microbiological laboratory. An NTS bacteraemia

episode was defined as beginning on the date of the first positive blood culture, regardless of NTS detected in other specimen types. Subsequent NTS-positive specimens from the same patient were omitted, except if >180 days had elapsed between two consecutive NTS-positive specimens. In this situation a new episode was recorded.

Numbers of NTS episodes per month were clustered over the 10-year study period. To equalize the differences in days per month, we calculated the adjusted number of days as  $30 n/a$ , where  $n$  is the clustered number of NTS episodes per month and  $a$  is the days per actual month (February adjusted for leap years).

We computed peak-to-trough (PTT) ratios with exact 95% confidence intervals, using the methodology described by Frangakis & Varadhan [18], and implemented in the 'R' language and environment for statistical computing, version 2.1.0 [19]. The underlying model assumes that monthly incidence rates perform a single annual cycle that can be modelled using a sinusoid. The method applies a sampling technique (we used 40 000 as the sample size) to yield exact 95% confidence intervals for the PTT ratio, along with a location (date) of the peak.

Initially, seasonal variation analyses were performed separately for three groups: GE patients (i.e. NTS found only in stool specimens) who were not hospitalized (outpatients), GE patients who were hospitalized (in-patients), and bacteraemia patients (all of whom were in-patients). Within each group, data were stratified by age group [<15, 15–64 (with these two groups merged for bacteraemia patients), and >64 years], comorbidity level (0 and  $\geq 1$  Charlson points), serotypes [*S. Enteritidis*, *S. Typhimurium* (with these two serotypes merged for bacteraemia patients), and others], and, for GE outpatients, by calendar year. Seasonal analyses were performed repeatedly to assess consistency of results.

## RESULTS

We identified 2086 patients and 2095 NTS infection episodes (1490 GE outpatients, 492 GE in-patients, and 113 bacteraemia in-patients) during the study period. The annual number of NTS infection episodes ranged from 138 in 2003 to 274 in 1997 (data not shown).

With increasing severity of NTS infections, elderly patients (especially those aged >64 years) and

patients with higher comorbidity levels were encountered relatively more often (Table).

In January–March, the more severe NTS infections occurred more often, and this was reversed in April–October (Fig.). The main divergence was seen between bacteraemia in-patients on the one hand and the two other patient groups on the other (Fig.).

The PTT ratio declined with increasing severity of NTS infection (Table). Stratified analyses showed consistent PTT ratios within each of the three groups, except that higher PTT ratios were seen in 15- to 64-year-old GE outpatients and in GE outpatients with *S. Typhimurium*. For GE outpatients, none of the 95% confidence intervals for the PTT ratios in each of the years 1994–2003 included '1' (data not shown).

The peak dates for GE outpatients and GE in-patients ranged from 31 July to 21 August, both in overall and stratified analyses (Table). For bacteraemia patients, the overall peak date (20 September) fell later than that for GE patients, and some peak dates in the stratified analyses differed from the overall peak date, e.g. mid-November for the >64 years age group and for patients having *S. Enteritidis* or *S. Typhimurium*. In the years 1994–2003, two peak dates for GE outpatients fell in July and eight peak dates fell in August (data not shown).

## DISCUSSION

Explanations for seasonal disease variation are generally divided into weather conditions, host-related characteristics, and, for infectious diseases, appearance and disappearance of the infectious agent [20]. Curiously, little is known about the specific impact of host characteristics on seasonal disease variation in humans, because most research has involved animals with distinct annual cycles (often related to reproduction), from which results are difficult to extrapolate [20, 21]. Our study does not differ from other human seasonal variation studies that describe real-life situations in which the complexity and interrelationship between specific factors are difficult to elucidate [20]. With regard to NTS several studies have reported a distinct seasonal variation with higher occurrence in the warmer months [1–7], but to our knowledge no study has related this to host characteristics, except for age [3, 7]. We hypothesized that the acquisition and pathogenesis of more severe NTS infections in debilitated patients was more related to endogenous host characteristics than in

Table. Peak-to-trough ratios (95% confidence intervals) and peak dates for patient groups (overall and stratified by age groups, Charlson comorbidity points [17], and main serotypes), based on adjusted monthly numbers of non-typhoid *Salmonella* episodes in North Jutland County, Denmark, clustered over the period 1994–2003

Analysis group	Gastroenteritis outpatients			Gastroenteritis in-patients			Bacteraemia patients		
	No. (%)	PTT (95% CI) <sup>a</sup>	Peak date	No. (%)	PTT (95% CI)	Peak date	No. (%)	PTT (95% CI)	Peak date
Overall	1490 (100) <sup>b</sup>	4.3 (3.6–5.0)	13 Aug.	492 (100)	3.2 (2.4–4.2)	12 Aug.	113 (100) <sup>c</sup>	1.6 (1.0–2.8)	20 Sep.
Age (years)									
<15	321 (21.8)	3.0 (2.2–4.2)	15 Aug.	123 (25.0)	3.0 (1.8–5.2)	31 July	57 (50.4) <sup>d</sup>	2.3 (1.0–5.0)	28 July
15–64	1016 (69.0)	4.8 (3.9–5.8)	12 Aug.	269 (54.7)	3.3 (2.3–4.7)	15 Aug.			
>64	135 (9.2)	3.4 (2.0–5.6)	20 Aug.	100 (20.3)	3.4 (1.9–6.2)	21 Aug.	56 (49.6)	2.3 (1.0–5.0)	16 Nov.
Comorbidity									
0 points	1370 (93.1)	4.3 (3.6–5.1)	13 Aug.	422 (85.8)	3.2 (2.4–4.1)	12 Aug.	68 (61.3)	2.3 (1.0–4.7)	18 Aug.
≥1 points	102 (6.9)	2.9 (1.7–5.2)	9 Aug.	70 (14.2)	2.9 (1.5–5.9)	10 Aug.	43 (38.7)	1.7 (1.0–4.0)	16 Dec.
Serotype									
<i>S. Ent.</i> <sup>e</sup>	781 (52.4)	4.2 (3.4–5.3)	13 Aug.	248 (50.4)	3.6 (2.5–5.3)	11 Aug.	72 (63.7) <sup>g</sup>	1.6 (1.0–3.2)	6 Nov.
<i>S. Typh.</i> <sup>f</sup>	362 (24.3)	5.7 (4.0–7.9)	17 Aug.	156 (31.7)	2.5 (1.6–4.0)	19 Aug.			
Other <sup>h</sup>	347 (23.3)	3.3 (2.4–4.5)	9 Aug.	88 (17.9)	3.5 (2.0–6.7)	9 Aug.	41 (36.3)	2.7 (1.0–6.8)	10 Aug.

<sup>a</sup> Peak-to-trough ratio (95% confidence intervals).

<sup>b</sup> Age and Charlson comorbidity points were unknown for 18 episodes ( $n = 1472$ ).

<sup>c</sup> Charlson comorbidity points were unknown for 2 episodes ( $n = 111$ ).

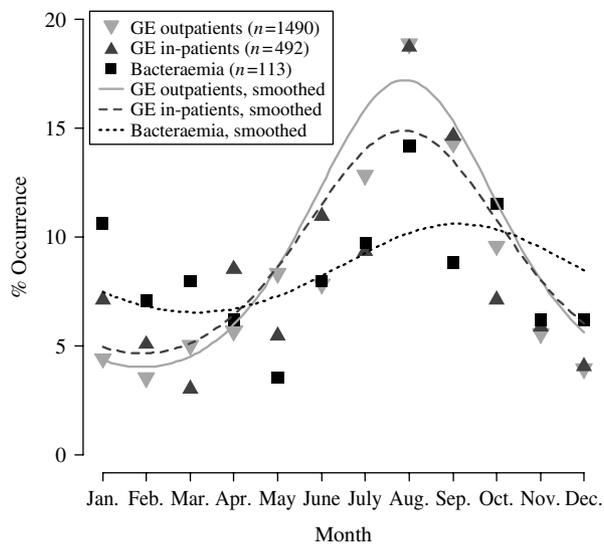
<sup>d</sup> <15 years ( $n = 9$ ) and 15–64 years ( $n = 48$ ) merged.

<sup>e</sup> *Salmonella (S.)* Enteritidis.

<sup>f</sup> *S. Typhimurium*.

<sup>g</sup> *S. Enteritidis* ( $n = 54$ ) and *S. Typhimurium* ( $n = 18$ ) merged.

<sup>h</sup> All other non-typhoid serotypes than *S. Enteritidis* and *S. Typhimurium*.



**Fig.** Monthly % occurrence (100×adjusted monthly numbers/adjusted annual numbers) of non-typhoid *Salmonella* infection episodes with corresponding estimated curves superimposed for three patient groups [gastroenteritis (GE) outpatients, GE in-patients, and bacteraemia patients], North Jutland County, Denmark, 1994–2003.

healthier patients in whom exogenous factors may be more crucial. Endogenous host characteristics, such as age and chronic diseases, do generally not show seasonal variation, whereas some exogenous factors related to NTS infections (e.g. travelling or barbecuing) occur more often in the warmer months.

We found that increased severity of NTS infection was associated with less seasonal variation. Age and level of comorbidity, both endogenous factors, also rose with more severe NTS infections, which indicates that exogenous factors were less important in the pathogenesis of more severe NTS infections. Conspicuously, 25 of the 43 (58%) bacteraemia patients with comorbid diseases had a diagnosis of coronary heart disease, cerebral infarction, or chronic pulmonary disease (data not shown). These diseases occur more commonly in the colder months or they are exacerbated by respiratory infections which are also more common in winter time [20, 22–24]. However, we had insufficient information to investigate the impact of specific comorbid diseases on seasonal NTS variation. Similarly, we could not investigate whether the more severely NTS infected patients tended to be exposed less to seasonal factors such as travelling or barbecuing. Among GE outpatients, a more pronounced seasonal variation was seen in the 15–64 years age group, compared with younger and older patients, a trend also reported from five

European countries (including Denmark) [7], but not from the United States [3], although more detailed studies are needed to evaluate possible reasons for these differences.

To our knowledge, few other studies have related the seasonal NTS variation to severity of infection. An US study of 8018 *Salmonella* bacteraemia isolates submitted from 1968 to 1979, reported a similar seasonal variation for stool and blood specimens [25]. However, different surveillance systems and reporting rates, other serotypes (including typhoid *Salmonella*), and the more varied climate in a larger country make comparisons difficult.

We clustered data over a 10-year period, during which the epidemiology of *Salmonella* in Denmark changed in terms of infection sources and serotypes. At the beginning of the study period, *S. Enteritidis* increased as part of a global pandemic [26], and it decreased after 1997 [5]. Similarly, NTS infection sources changed over time; the risk from broiler meat and pork diminished and the risk from eggs increased [5, 27]. In spite of these and other putative changes during the study period, we found that seasonal variation for GE outpatients remained quite constant from year to year.

The seasonal variation analysis we employed is based on the assumption that all NTS episodes are independent of each other, i.e. they occurred as sporadic episodes, and not as part of outbreaks. We estimated that 4–11% of the Danish NTS cases were associated with outbreaks [5, 28], a range similar to that reported for other countries [2] despite different surveillance systems and definitions of outbreaks. If outbreaks are distributed unevenly throughout the year, seasonal variation among GE outpatients will be affected most, since GE in-patients, and in particular bacteraemia patients, constitute minorities in outbreaks, i.e. their episodes *per se* are more sporadic. If the seasonal variation of outbreaks follows the general seasonal variation, this bias will strengthen the distinct seasonal variation observed amongst GE outpatients; however, evidence is sparse on the seasonality of outbreaks.

One limitation of our study was the relatively small number of bacteraemia in-patients. However, some stratified seasonal GE outpatient and GE in-patient analyses that relied on similarly low numbers did confirm the distinct seasonal variation seen in these patient groups overall.

Another limitation is that data used in our study were generated from a passive surveillance system.

To our knowledge, ratios between recorded and actual NTS infection cases have only been estimated in two studies, one from the United Kingdom (ratio 3.2) [29], the other from the United States (ratio 38) [30]. A higher proportion of NTS infections will probably go undetected as the severity declines [31]. A constant ratio between recorded and actual NTS cases throughout the year would not bias our results. However, increased vigilance among patients and physicians towards NTS infections during certain periods, e.g. shortly after travel abroad, may contribute to higher seasonal variation. This probably occurs mainly for patients with the less severe NTS infections, leading to an overestimation of PTT ratios in this group. Other inaccuracies, such as a few 1994–1997 patients classified as GE patients who possibly had specimen types other than stool, lead time between NTS symptom onset and specimen receipt dates, and the definition of an NTS episode, are believed to be minor, without an influence on the main trends reported here.

In conclusion, we detected a trend of less seasonal variation of NTS infections (with peaks and troughs occurring in the warmer and colder months respectively) concurrently with higher severity of NTS infection. This could indicate that endogenous factors play a more pivotal role than exogenous factors in the occurrence of severe NTS infections and/or patients with more severe NTS infections engage less in activities that increase the risk of acquiring NTS infections in the warmer months (e.g. travelling or barbecuing). Further studies combining surveillance and clinical data are needed to examine these assumptions.

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#### DECLARATION OF INTEREST

None.

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