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Salmonellosis in North Thames (East), UK: associated risk factors

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SUMMARY

We assessed the rate of salmonella infections and risk factors associated with infection in North East Thames in 1993. Cases of culture confirmed infection were identified through microbiology laboratories and environmental health officers in the North East Thames. A total of 1730 cases were reported and 209 of these individuals (those who could be contacted within a 3-week interval after onset of symptoms) and matched controls were interviewed by telephone. In addition randomly selected controls were interviewed over a 4-month period about recent gastric acid lowering medication and antimicrobial ingestion. Sixty-six serotypes were identified: *S. enteritidis* was isolated from 1179 (69%) cases, *S. typhimurium* from 221 (13%), *S. virchow* from 77 (4%) and *S. newport* 25 (1%). Infections were more frequent in summer months. Highest rates were documented in children under 2 years of age for *S. enteritidis* (108/100000) and under 1 year for *S. typhimurium* (36/100000). Using the Townsend score, highest isolation rates of *S. enteritidis* were in more prosperous areas (36/100000 *vs.* 27/100000; odds ratio (OR) 1·3, 95% confidence intervals (CIs) 1·2–1·6, $P < 0{\cdot}0001$), while for *S. typhimurium*, there was no relation between deprivation index and isolation rates areas (6·4/100000 *vs.* 6·1/100000; OR 1·1, 95% CIs 0·8–1·5, $P = 0{\cdot}77$). The case control study showed a significant association between ingestion of products containing raw eggs and *S. enteritidis* infection (8/111 cases *vs.* 0/110 controls; OR undefined, lower 95% CIs 3·4). Individuals with salmonella infection were significantly more likely to have travelled abroad in the week before the onset of illness [42/186 (23%) *vs.* 1/182 (0·5%); OR 40, 95% CIs = 5·5–291, $P < 0{\cdot}001$] and to report gastroduodenal disease [11/143 (7%) *vs.* 3/143 (2%); OR 5·0, 95% CIs = 1·1–23, $P = 0{\cdot}04$]. There was an association between illness and gastric acid-lowering medications [unmatched controls OR 22·3 (95% CIs 1·5–3·7, $P = 0{\cdot}0002$), matched controls OR 3·7 (95% CIs 1·0–3·8, $P = 0{\cdot}07$)], but no association with antimicrobial ingestion.

INTRODUCTION

Risk factors for salmonellosis have been predominantly identified during outbreak investigations including the association of some serotypes with specific vehicles [1–4]. Although risk factors can be identified using case control studies with sporadic cases [5] and among those associated with outbreaks, it is difficult to decide whether to match for neighbourhood, general practice, or to use randomly selected controls. Individuals who are part of a cluster may be more likely to be identified than those not associated with clusters, but it is unclear whether such individuals are typical of sporadic salmonellosis.

There may be factors between countries that affect the risks, such that similar studies from different countries might yield divergent results. In this prospective study, we investigated risk factors for spor-

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adic salmonellosis, including age, socio-economic status, foreign travel and prior ingestion of gastric acid-reducing agents (antacids, H_2 antagonists or proton pump inhibitors) or antimicrobials.

METHODS

Case definition

A case of salmonella infection was defined as an individual residing in North Thames (East) Region (NTER) from whom an isolate of salmonella was obtained in 1993.

Case finding

Individuals fulfilling the case definition were identified by the 19 microbiology laboratories and environmental health officers in the NTER. Laboratories and environmental health officers were contacted weekly to identify salmonella cultures. The serotype and patient identifying details were forwarded for each patient.

For each patient an attempt to identify a telephone number was made through British Telecom Directory Enquiries. Once the telephone number was obtained, an attempt was made to contact the individual or, if a child, the parent. This enabled a food and travel history to be obtained for the food ingested in the 3 days prior to illness. In addition, a full history of prescribed and over-the-counter medications was obtained for the months prior to illness. A question on long-term illness was also included. From these data, we were able to determine which individuals had ingested gastric acid-reducing medication prior to the onset of illness. Where a patient was unsure of the medication being taken, information was obtained from the patient's general practitioner.

Comparison group

Two comparison groups were used to provide controls for the case-control study:

(1) *Case-nominated controls*. Controls were matched for age, gender and area of residence, and were interviewed by telephone. Controls were asked about exposures for the time frame up to the date of interview. All case-patients were eligible to be included in the case-nominated case-control study if contact was made with the patient less than 3 weeks prior to onset of illness.

(2) *Randomly selected controls from the greater London area*. These controls were interviewed by the Omnibus Survey of the Offices of Population Censuses and Surveys between October 1992 and January 1993. Individuals were specifically questioned to identify rates of diarrhoea, stool culture, antimicrobial and gastric acid-lowering medication use in persons over 15 years of age throughout Great Britain [6]. Of the 8143 individuals interviewed in the original study, 931 (11·5%) lived in greater London. Seventy-seven (8%) of the 931 individuals were excluded as they reported diarrhoea in the last month. Thus a total of 854 controls were available for analysis. The methods for the Omnibus survey have been described in detail elsewhere [7].

Denominators

Age-specific rates were computed using mid-year 1991 ward-based population estimates. The under-5 population was from 1991 census local base statistics.

Socio-economic rates were calculated using the 1991 OPCS census for wards (average ward population in NTER = 6688) for NTER for those census variables that comprise the Townsend score together with population figures. The 1991 ward boundaries for NTER were obtained from OPCS. The population in two enumeration districts straddling the borders of NTER and East Anglia Region were excluded. Deprivation scores were calculated for each ward using the method described by Townsend [8]. The postcodes (UK address codings similar to the United States zip codes) of all reported cases were linked to the wards. NETR wards were grouped into three equal sized groups according to Townsend score (deprived, intermediate and less deprived) and each case ascribed to a Townsend group.

Statistical methods

Unmatched case-control calculations prior to the study suggested if the prevalence of antimicrobial or antacid use among the general population was 4%, 200 case-control pairs would enable a statistically significant difference at the 0·05% level with 80% power if the prevalence of antimicrobial or antacid ingestion in those with salmonella infection was 12% [odds ratio (OR) = 3·3]. In the randomly selected case-control study with over four randomly selected controls per case a statistically significant difference at the 0·05% level with 80% power would be observed if the prevalence of antimicrobial or gastric acid lower medication in those with salmonella infection was 9·5% (OR = 2·5).

For the analysis of socio-economic status, rates of salmonella infection in deprived and prosperous wards were compared. χ^2 tests and χ^2 tests for linear trend were calculated using Epi-Info 6 (CDC, Atlanta, GA, USA).

Epi-Info 6 was used for both matched and non-matched analysis to compare exposures between case and comparison groups. In the unmatched analysis all those less than 16 years of age were excluded. Exact 95% confidence intervals (CIs) were calculated using the procedure described by Thomas and Gart [9].

To reduce the likelihood that cases were associated with clustering or foreign travel, we conducted the analysis both with and without such cases. Clustering was defined as two or more cases with the same postcode, same serotype and phagetype, and onset dates within one calendar month. Cases reporting foreign travel were also excluded.

RESULTS

In NTER in 1993, 1730 cases of salmonellosis were reported. Sixty-six serotypes were identified and from 6 individuals 2 serotypes were identified. *S. enteritidis* was isolated from 1196 individuals (69·1%), *S. typhimurium* from 229 (13·2%), *S. virchow* from 76 (4·4%) and *S. newport* from 25 (1·4%). Salmonella infections were most frequent in the summer months (Fig. 1). Ninety-two percent of postcodes were recorded only once (Table 1).

Highest age-specific isolation rates for *S. enteritidis* (108/100000) were in those aged under 2 years and for *S. typhimurium* (36/100000) in those under 1 year. Rates again increased among those over 85 years of age (Table 2, Fig. 2). Among those less than 1 year of age there were no peak age-specific rates for either serotype. Median age for *S. enteritidis* was 27 years while that for *S. typhimurium* was 20 years (Kruskal–Wallis H test 24·4, $P > 0{\cdot}0001$).

Social deprivation

Isolation rates of *S. enteritidis* were significantly higher in more prosperous wards, while for *S. typhimurium*, there was no relation between deprivation index and isolation rates (Table 3).

Case-control study

Two hundred and nine patients were interviewed by telephone, of whom 23 were considered part of 10 clusters and 43 reported overseas travel. Sixteen serotypes were represented among these patients: *S. enteritidis* was isolated from 152 (72·7%) individuals, *S. typhimurium* from 26 (12·4%), *S. virchow* from 11 (5·3%) and *S. newport* from 5 (2·4%). These proportions were similar to those seen among all patients. Individuals with salmonella infection were significantly more likely to have reported travel abroad in the week before the onset of illness than controls [42/186 (23%) *vs*. 1/182 (0·5%), OR 40, 95% CIs 5·5–291, $P < 0{\cdot}001$]. There was no statistical difference in frequency of overseas travel between individuals with *S. enteritidis* [21/133 (16%)] and *S. typhimurium* [5/22 (23%)], $P = 0{\cdot}5$. Overseas travel among patients with serotypes other than *S. enteritidis* and *S. typhimurium* was significantly more frequent [16/31 (52%), $P < 0{\cdot}001$].

After removing clustered cases and those reporting overseas travel, there remained 143 cases. Of these, 69 (24%) were under 16 years of age. Seventy-eight percent were *S. enteritidis*, 12% *S. typhimurium* and 4% *S. virchow*, proportions that were similar to the

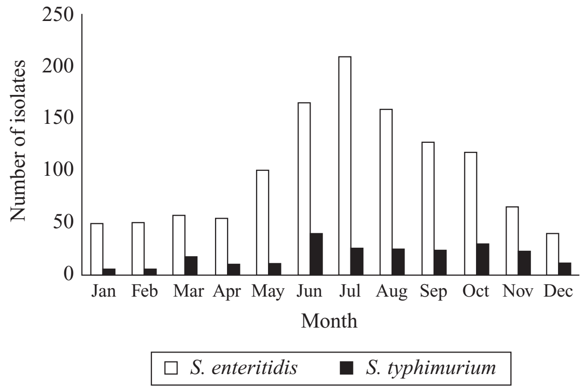

Fig. 1. Month of onset of cases for the two most frequent salmonella serotypes, North Thames (East) Region, 1993.

Table 1. *Frequency of postcodes identified for salmonella cases, North Thames (East) Region, 1993*

Number of times postcode recorded	Frequency	
	n	%
1	1419	92·0
2	93	6·0
3	17	1·1
4	8	0·5
5	3	0·2
8	1	0·06
16	1	0·06
Total	1542	100

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Table 2. S. enteritidis *and* S. typhimurium *culture-positive rates by age, North Thames (East) Region, 1993*

Age group (years)	*S. enteritidis*		*S. typhimurium*		Other salmonellae		Total		
	n	Rate/100 000	*n*	Rate/100 000	*n*	Rate/100000	*n*	Rate/100000	Denominator
0	58	104·5	20	36·0	31	55·8	109	196·3	55524
1	59	107·8	15	27·4	22	40·2	96	176·4	54720
2	49	91·5	10	18·7	12	22·4	71	132·5	53566
3	50	93·9	8	15·0	10	18·7	68	127·0	53271
4	34	66·5	11	21·5	2	39	47	91·9	51152
5–14	133	28·8	33	7·1	22	4·8	188	40·7	462444
15–24	138	25·2	40	7·3	39	7·1	217	39·6	547658
25–44	339	28·7	54	4·6	100	8·5	493	41·7	1183095
45–64	220	28·7	21	2·7	48	6·3	289	37·7	767166
65–74	50	16·3	5	1·6	8	2·6	63	20·6	306127
75–84	31	15·9	2	1·0	5	2·6	38	19·5	195301
85+	18	32·2	2	3·6	31	55·4	51	91·2	55930
Total	1179	31·1	221	5·8	330	8·7	1730	45·7	3785954

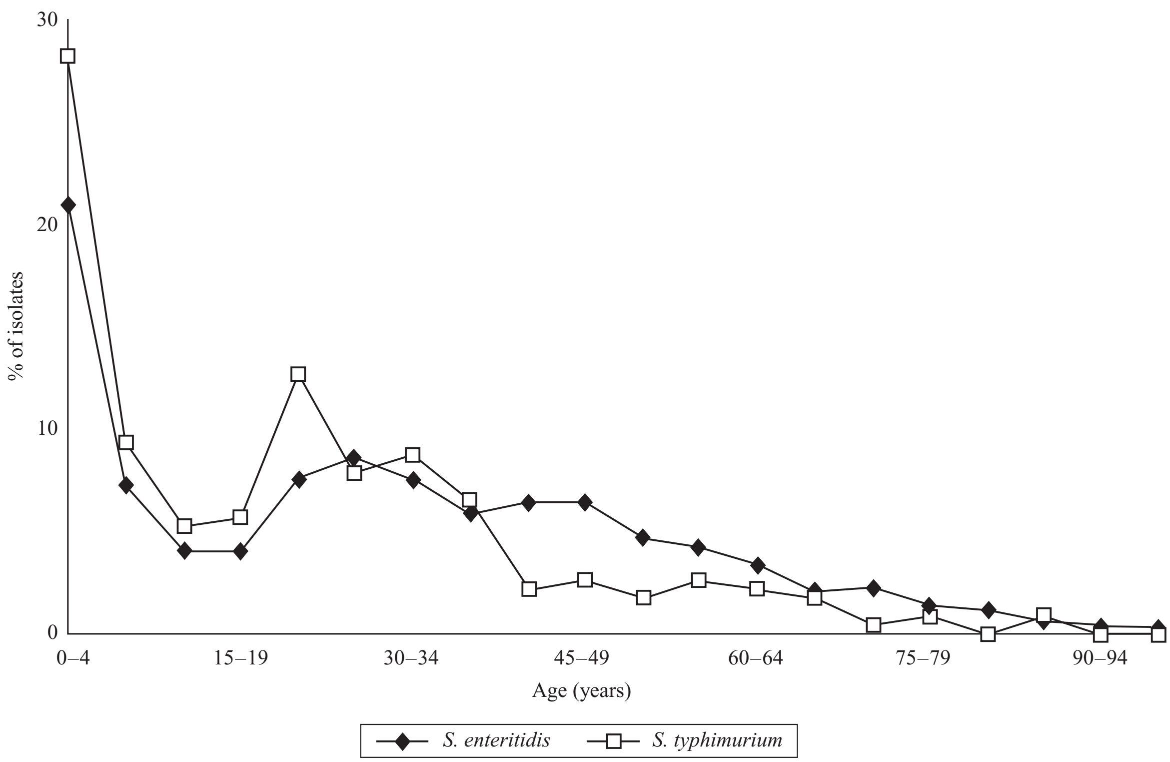

Fig. 2. Age distribution for *S. enteritidis* and *S. typhimurium* infections, North Thames (East) Region, 1993.

total serotypes reported. None of the cases or controls reported gastric surgery.

Among the 143 cases, use of gastric acid reducing medication increased with age [less than 5 years, 0/18 (0%); 5–15 years, 0/16 (0%); 16–44 years, 12/67 (18%); 45–64 years, 13/33 (39%) and greater than 64 years, 5/9 (56%); χ^2 trend 20·5, $P < 0·0001$]. Such a pattern was not seen with antimicrobial use: [less than 5 years, 2/18 (13%); 5–15 years, 2/16 (11%); 16–44 years, 6/67 (9%); 45–64 years, 4/33 (12%) and greater than 64 years, 1/9 (11%); χ^2 trend 0·001, $P = 1·0$]. There was no seasonal association between either gastric acid-reducing medication or antimicrobial ingestion.

There was an association between prior ingestion of gastric acid-lowering drugs and salmonella infection (Table 4). The association persisted with similar orders of magnitude for both matched and unmatched

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Table 3. S. enteritidis *and* S. typhimurium *isolation rates according to Townsend score, North Thames (East) Region, 1993*

	S. enteritidis		*S. typhimurium*		
Level of deprivation	*n*	Rate/100000	*n*	Rate/100000	Denominator
Deprived	433	27·1	97	6·1	1600933
Intermediate	432	32·8	68	5·2	1316079
Prosperous	314	36·1	56	6·4	868942
Total	1179	31·1	221	5·8	3785954
Odds ratio* (95% CI)	1·3 (1·2–1·6)		1·1 (0·8–1·5)		
χ^2 linear trend	$P < 0·0001$		$P = 0·8$		

* Comparing cases from prosperous wards with those from deprived wards.

Table 4. *Association between gastric acid-lowering medication, antimicrobial ingestion and salmonella infection*

	Proportion exposed			Proportion exposed		
Exposure	Cases	Case-nominated controls	Matched odds ratio (95% confidence intervals)	Cases (> 15 years)	Omnibus controls	Unmatched odds ratio (95% confidence intervals
Gastric acid-lowering drugs	30/143 (21%)	18/143 (13%)	1·9 (1·0–3·8)*	30/109 (28%)	92/854 (11%)	3·2 (1·9–5·2)†
Antimicrobial drugs	15/143 (10%)	12/143 (8)	1·3 (0·6–2·8)	11/109 (10%)	69/854 (8%)	1·3 (0·6–2·6)

* $P = 0·07$.
† $P < 0·0001$.

Table 5. *Association between chicken, beef and raw shell egg consumption in cases and controls*

	S. enteritidis			*S. typhimurium*		
	Proportion exposed			Proportion exposed		
Exposure	Cases	Controls	Matched odds ratio (95% confidence intervals)	Cases	Controls	Matched odds ratio (95% confidence intervals)
Chicken	60/111 (54%)	55/110 (50%)	1·2 (0·7–2·0)	7/17 (41%)	9/17 (53%)	0·6 (0·1–2·5)
Beef	33/111 (30%)	49/110 (45%)	0·6 (0·3–1·0)*	8/17 (47%)	10/17 (59%)	0·6 (0·1–2·5)
Raw eggs	8/11 (7%)	0/110 (0%)	undefined (lower limits = 3·4)†	0/17 (0%)	0/17 (0%)	1·0

* $P = 0·04$.
† $P = 0·02$.

controls when cases clustering and reporting overseas travel were included in the dataset [unmatched controls OR 2·3 (95% CIs 1·5–3·7, $P = 0·0002$), matched controls OR 3·7 (95% CIs 1·0 to 5·8, $P = 0·07$)]. There was however, no association between prior antimicrobial use and salmonella infection for either set of controls (Table 4). This lack of association persisted for both matched and unmatched controls when cases clustering and reporting overseas travel were included in the dataset.

There was a statistical association between consuming products containing raw shell egg in the 3 days before illness for *S. enteritidis* infection. No such association was seen for *S. typhimurium* (Table 5). Cases of *S. enteritidis* were significantly less likely than controls to consume beef over the same period. There was no relationship between either *S. enteritidis* or *S. typhimurium* and consumption of chicken (Table 5).

Cases were significantly more likely to report a long term illness than matched controls [46/143 (32%) *vs.*

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23/143 (16%); OR 2·7, 95% CIs = 1·4–5·0, P = 0·002]. When long-term illness was confined to gastric or duodenal ulcer disease, gastritis, heartburn or oesophagitis cases remained more likely than controls to report these conditions [11/143 (7%) *vs*. 3/143 (2%); OR 5·0, 95% CIs = 1·1–23, $P = 0·04$]. All individuals reporting diabetes mellitus, malignancy or immunodeficiency ($n = 5$) were cases.

DISCUSSION

There are four major findings from this study. First, the very young and over 85s were at greater risk for culture-positive *S. enteritidis* and *S. typhimurium* infection. Second, *S. enteritidis*, unlike *S. typhimurium* appears to be more frequent among populations living in less deprived areas. Third, an association was seen between illness and ingestion of gastric acid-lowering medication in the 4 weeks before the onset of illness and fourth, no association was seen between illness and recent ingestion of antimicrobial agents. As it is possible that individuals who were part of a cluster, or who had recent travel overseas ingested differing doses of salmonella from sporadic cases, we conducted our analysis both with and without these cases, but this had no significant effects on the results.

It is difficult to be certain whether the higher rates at the extremes of age are a true measure of increased risk or result from an increased frequency of culture. Children and the elderly with diarrhoea may be expected to be cultured more frequently than other age groups. In a recent study based on UK adults, stool culture following an episode of diarrhoea was no more frequent among the elderly than younger adults (R. Feldman, N. Banatvala, personal observation).

In this study, cases did not have individual measures of socio-economic status. Individuals were described on the basis of measures of deprivation for the area in which they resided. The association between socio-economic status and *S. enteritidis* is unlikely to be explained by bias. Those requesting stool culture have no knowledge of serotype. Since specific serotypes are associated with particular vehicles, it may be that those from populations living in less deprived areas more frequently ingest vehicles harbouring viable *S. enteritidis* infection, such as between ingestion of products containing raw egg. Since travel overseas was associated with infection, the association with more prosperous areas may be a reflection of travel. However, in the case-control study, there was no association between travel and either *S. enteritidis* or *S. typhimurium*, and this suggests the association between social deprivation and *S. enteritidis* is unlikely to be explained by travel.

The case-control study demonstrated an association between salmonella infection and prior ingestion of gastric acid-lowering drugs in the 4 weeks before the onset of illness. This was also found in a study of sporadic salmonellosis in Nottingham, UK [10]. No association was observed between salmonellosis and recent antimicrobial ingestion in any age group although outbreak investigations have suggested this as a significant risk factor [11]. In Nottingham, antimicrobial use was a significant risk factor in those over 65 years only [10]; an age group that made up a significant proportion of their study. The unmatched study used a 4-month period over winter. It might be that antimicrobial ingestion rates were higher during this period in controls than the rates in cases which were obtained over a calendar year. However, among cases, we failed to detect any difference in rates of antimicrobial use by month of illness onset.

Only those individuals with salmonella cultured from stool were included in the study. Patients with salmonella infection who did not have salmonella isolated by a laboratory were not included and this group would for example include: (*a*) those that failed to attend a GP; (*b*) those who saw their GP but were not requested to forward stool for examination; and (*c*) those where stool was taken but inappropriately stored or microbiologically handled. The patients included in the study thus reflect a highly select subset of patients with salmonella infection and may reflect those with more severe symptoms or those with an illness of a longer duration. Cultured cases may also be different from other patients with salmonella infection with respect to age at illness, travel, level of social deprivation, gastric or other risk factors. If particular GPs were more likely to culture patients, then individuals from such practices, with their particular geographic or other characteristics would be over-represented in this study.

The patients included in the case-control studies are even more select. These were patients from whom salmonella was cultured, whose telephone number we could obtain, and who we could subsequently contact and interview within 3 weeks of the onset of the illness. Since the research was predominantly carried out during day hours, interviewees would be those less likely to be working outside the home. The case-control studies used only 12% of patients reported in the study. Obtaining telephone numbers was not usually a difficulty and we were able to identify telephone numbers on the majority of cases reported to use before the 3-week deadline. The major difficulty was that many patients were not available for interview during the day (workload was such that sampling methods were not required to determine which patients to interview). Although not quantified, we did not suspect that particular districts or laboratories were more or less likely to have their cases reported in a particular time frame, or particular serotypes, or patient groups be reported less quickly.

Although case-nominated controls are a potentially biased group to use in a case-control study [12], it was interesting that similar associations with regard to infection and antimicrobial and gastric acid lowering drugs were detected in both case-control studies. Interviews conducted by telephone have been reviewed in detail [13] and appear to have equal accuracy rates to face-to face interviews in relation to the collection of data on general health status. There is the potential of over-representing people who are most likely to be at home (and who answer the telephone). Surveys using telephone interviews have been popular for many years in the USA, where levels of telephone ownership are high, and also among market researchers. They are slowly becoming more popular among social researchers in Europe, although they have the disadvantage that people in lower socio-economic groups have lower rates of telephone ownership. Although there may be some bias introduced by this approach, the variable used in this study was not the social class status of individuals but the Townsend score of the ward in which they lived.

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