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Dose–response effects in an outbreak of *Salmonella enteritidis*

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SUMMARY

The effects of ingested *Salmonella enteritidis* (SE) dose on incubation period and on the severity and duration of illness were estimated in a cohort of 169 persons who developed gastroenteritis after eating hollandaise sauce made from grade-A shell eggs. The cohort was divided into three groups based on self-reported dose of sauce ingested. As dose increased, median incubation period decreased (37 h in the low exposure group *v.* 21 h in the medium exposure group *v.* 17·5 h in the high exposure group, $P = 0{\cdot}006$) and greater proportions reported body aches (71 *v.* 85 *v.* 94%, $P = 0{\cdot}0009$) and vomiting (21 *v.* 56 *v.* 57%, $P = 0{\cdot}002$). Among 118 case-persons who completed a follow-up questionnaire, increased dose was associated with increases in median weight loss in kilograms (3·2 *v.* 4·5 *v.* 5·0, $P = 0{\cdot}0001$), maximum daily number of stools (12·5 *v.* 15·0 *v.* 20·0, $P = 0{\cdot}02$), subjective rating of illness severity ($P = 0{\cdot}0007$), and the number of days of confinement to bed (3·0 *v.* 6·5 *v.* 6·5, $P = 0{\cdot}04$). In this outbreak, ingested dose was an important determinant of the incubation period, symptoms and severity of acute salmonellosis.

INTRODUCTION

In 1970, higher attack rates and shorter incubation periods were reported for volunteers fed increasingly larger doses of *Salmonella typhi* [1]. The clinical course, once illness occurred, did not vary with the dose of infectious inoculum. For acute non-typhoidal salmonellosis, the relations between inoculum, incubation period, and clinical course are less well characterized [2]. In experimental studies of volunteers fed several different non-typhi *Salmonella* serotypes, larger inocula resulted in higher attack rates and tended to result in higher rates of vomiting and hospitalization, but clear relations between inoculum, incubation period and other symptoms were not apparent [3–5].

Relations between dose, incubation period, and clinical course have been sought

in observational studies. In an outbreak of gastroenteritis caused by *Salmonella typhimurium*, incubation periods were shorter and muscle pains more prevalent among persons who ate more contaminated chicken. Shorter incubation periods were associated with vomiting, fever, abdominal pain, chills, hospitalization, symptom duration, the amount of time taken off from work, and other markers of severity, but a direct relation between dose (the quantity of chicken consumed) and severity of illness could not be shown [6]. In two recently reported outbreaks of gastroenteritis caused by *Salmonella* serotype *enteritidis* (SE), a correlation was noted between shorter incubation period, greater likelihood of hospitalization, and delayed ingestion of the implicated food (a proxy measure for increased dose), but symptom frequency and severity were not described [7, 8]. We report the effects of estimated SE dose on incubation period and on the presence, severity and duration of specific symptoms following a large outbreak of SE gastroenteritis with an extremely high attack rate.

BACKGROUND

On 2 June 1990, a hospital nurse reported 10 patients with food poisoning to a local health department. All 10 patients had attended a wedding reception at a hotel on 1 June. The Connecticut Department of Health Services began an investigation on 4 June.

The only meal the initial patients reported in common was the reception dinner, prepared by five hotel chefs and six kitchen workers, and served between 20.30 and 21.30 h on 1 June to all 180 persons attending the reception. The dinner included an appetizer buffet, salads, vegetables, ice cream, wedding cake, and coffee in addition to a single main course, Chicken Oscar. According to the chefs, each serving of Chicken Oscar was topped with a measured 1-ounce portion of hollandaise sauce. The hollandaise sauce was prepared on 1 June from 150 extra-large grade-A shell eggs, delivered by refrigerated truck 3 days earlier and kept in the walk-in cooler. According to Chef A, who cracked and separated the eggs by hand at 19.30 h, none was soiled or broken. At 19.50 h, ten pounds of clarified butter at 93 °C and commercial lemon and lime juice were thoroughly mixed with the egg yolks in an automatic mixing bowl over low heat. At 20.05 h, the sauce was taste-tested by both Chef A and Chef B, covered with cellophane wrap, and kept warm until serving began. The chicken breasts were delivered frozen on 30 May, and were thawed, sautéed, and refrigerated on 31 May. On 1 June, at 19.30 h, they were baked at 117 °C for 25 min. Each chicken breast was then put on a dinner plate, garnished with crab meat and asparagus, and kept covered in a warming box at 71 °C. At 20.30 h, Chef B ladled 1 ounce of hollandaise sauce over each chicken breast and these were then served to the guests over an approximate 20-min period.

METHODS

Outbreak investigation

To determine the source of the outbreak, a questionnaire on food and beverage consumption, presence and time of onset of symptoms, and initial treatment was administered to all 180 attendees (176 by telephone and 4 by mail). A case was

defined as a reception guest who either developed diarrhoea ($\geqslant$ 3 loose stools in a 24-h period) or had a stool culture yielding SE between 1 June and 16 June.

Food preparation practices were reviewed and the hotel kitchen facilities were inspected on 2 June and 4 June. On 4 June, the 11 hotel workers who prepared the dinner were interviewed regarding illness the month before and 3 days following the reception, and each worker submitted a stool specimen for culture. On 18 June, the same 11 workers were reinterviewed about illness since the reception.

No leftover food items were available for testing. However, 10 dozen eggs from the batch used to make the hollandaise sauce were taken from the hotel kitchen walk-in cooler, incubated for 3 weeks at room temperature, and cultured for salmonella. The *Salmonella* Task Force of the United States Department of Agriculture (USDA) tested environmental samples from the three henhouses at the farm where the eggs originated and performed necropsy examination on 60 hens from each henhouse. Phagetyping of SE isolates obtained by the USDA was done at the National Veterinary Services Laboratory in Ames, Iowa. SE isolates from six case-patients were phagetyped by the Foodborne and Diarrheal Diseases Branch Laboratory of the Centers for Disease Control and Prevention (CDC) using the Ward system [9].

Investigation of dose–response effects

Respondents were asked the number or number of glasses consumed for each buffet item and beverage, and whether they had eaten 'none' 'some', 'most', or 'all' of each dinner item served. Patients were divided into three exposure groups according to reported consumption of the implicated food.

To collect more information on symptoms, treatment, and outcome, a second questionnaire was mailed to all patients 4 weeks after the reception. Clinical variables included the maximum number of loose stools in any 24-h period, acute weight loss in pounds, highest recorded temperature, and the subjective rating of illness severity as scored by patients on a scale from 1 to 10. Respondents were asked to indicate on a 4-week calender, for each day since the reception, whether they had diarrhoea or fever, limited their normal activities, remained bedridden, or were hospitalized.

Investigation of stool carriage rates

State health departments were contacted for information on initial clinical stool cultures. To measure carriage rate, all attendees from whom SE had been isolated on initial stool culture were sent faecal sample collection kits containing buffered glycerol saline 4 weeks after the reception. At the CDHS laboratory, faecal samples returned by mail were cultured for salmonella on XLD and MacConkey media alone and after incubation in selenite broth. Colonies were subcultured to TSI slants, confirmed biochemically, and serotyped. Resistance to ampicillin, amikacin, cefoxitin, cefuroxime, ciprofloxacin, gentamycin, tetracycline, and trimethoprim-sulfamethoxazole were determined for three original isolates and all repeat isolates by the Sensititre susceptibility system at the University of Connecticut Health Science Center.

Statistical analysis

Food-specific relative risks (RR), their 95% confidence intervals (CI) and Mantel–Haenszel p-values were calculated (Epi-Info, version 5.1). For the three exposure groups, binomial variables were compared by the Cochran–Armitage test for trend and median values of continuous variables were compared by the Jonckheere–Terpstra test for ordered alternatives (Statxact, version 1.0). One-sided exact p-values are reported for the Cochran–Armitage test and one-sided asymptotic p-values are reported for the Jonckheere–Terpstra test.

RESULTS

Outbreak investigation

Case description

Completed questionnaires were obtained from 178 persons attending the reception; 168 (94%) reported diarrhoeal illness. One guest denied diarrhoea but had abdominal cramps and a stool culture that yielded SE for a total of 169 cases and an attack rate (AR) of 95%.

Most patients reported abdominal cramps (94%), fever (90%) body aches (89%), headache (86%), nausea (79%), and vomiting (51%) (Table 1). Diarrhoeal onset occurred from 4 to 121 h after the midpoint of the reception dinner (median, 19 h; mean, 25 h) (Fig. 1).

According to data from both the initial and the follow-up questionnaires, 132 ill persons sought medical care, 95 had stool specimens collected for culture, 52 received intravenous fluids, 52 were treated with antibiotics, and 20 (at least 2 of whom were bacteraemic) were admitted to a hospital (Table 1). The mean length of hospitalization was 3·8 days (range 1–10 days). No deaths occurred.

The median patient age was 37 years; 92% were between 21 and 65 years of age. Only four persons had taken medications that may have affected host response: one was taking steroids (for rheumatoid arthritis) and three had taken antibiotics in the month before the wedding. None recalled taking antacids or H_2 blockers or reported an illness affecting the immune system.

Food-specific attack rates

All 169 case-patients and 5 of 9 well respondents reported eating the Chicken Oscar (RR undefined, $P < 0{\cdot}0001$); no other food item was strongly associated with illness. Two components of the Chicken Oscar, the chicken breasts (RR 6·9, $P < 0{\cdot}0001$) and the hollandaise sauce (RR 1·4, $P < 0{\cdot}001$), had the highest relative risks.

Eight respondents did not recall eating the chicken; of these, only two, both of whom ate the hollandaise sauce, met the case definition. All 169 patients reported eating either chicken breasts alone (29), hollandaise sauce alone (2), or both together (138). The hollandaise sauce was recognized and eaten by 144 persons, of whom 140 met the case definition (AR 97%). In some servings, time and temperature conditions permitted the hollandaise sauce to break down and be absorbed into the chicken, making it impossible to recognize the sauce, or to eat the chicken without at least some of the sauce. Under the assumption that every

Table 1. *Number and percentage of all patients reporting symptoms and medical interventions, percentage of all patients reporting symptoms by exposure group, and percentage of all survey respondents reporting medical interventions by exposure groups**

	All patients (n = 169)		All patients by exposure group			
			High (n = 109)	Medium (n = 27)	Low (n = 29)	Cochran–Armitage test for trend
Symptom	n	%	%	%	%	p value
Abdominal cramps	156	94	95	97	86	> 0·05
Fever	141	90	92	88	85	> 0·05
Body aches	149	87	94	85	71	0·001
Headache	146	86	88	93	76	> 0·05
Nausea	133	79	84	89	52	0·001
Vomiting	86	51	57	56	21	0·002
			Survey respondents by exposure group			
	All patients (n = 169)		High (n = 79)	Medium (n = 20)	Low (n = 19)	Cochran–Armitage test for trend
Intervention	n	%	%	%	%	p value
Physician visit	132	81	87	85	79	> 0·05
Hospitalization	20	13	14	20	5	> 0·05
Stool culture	95	60	65	70	47	> 0·05
Antibiotic treatment	51	32	37	25	42	> 0·05
Intravenous fluids	52	38	38	35	11	0·04

* Non-responders excluded from the analysis.

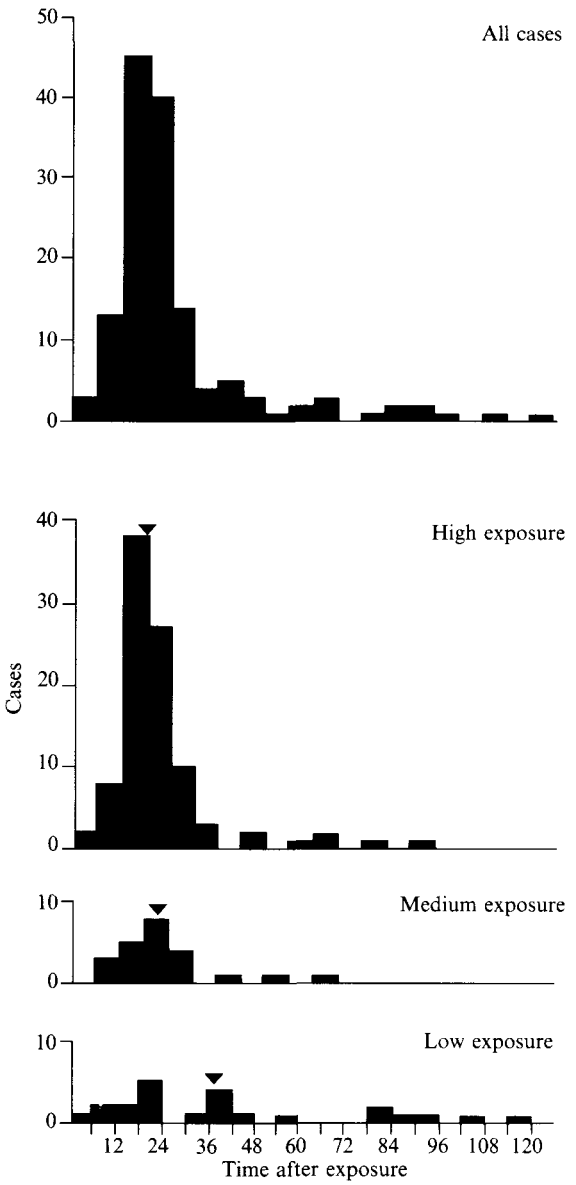

Fig. 1. Onset of diarrhoea by 6-h intervals: all cases and high-, medium-, and low-exposure groups. *Salmonella enteritidis* outbreak, Connecticut, 1990. ▼, Group median.

person who ate chicken also, knowingly or unknowingly, ate the hollandaise sauce, the attack rate for consumption of hollandaise sauce was 169/174 or 97%.

Food handlers and egg traceback

None of the 11 hotel workers who prepared the dinner reported diarrhoea, fever, or cramps when interviewed on 4 June; only one, Chef C, reported headaches and

body aches. When reinterviewed on 18 June, Chef C reported having had diarrhoea and Chef B reported stomach cramps, fever, and diarrhoea with onset on 9 June. SE was cultured from the stools of three workers; Chefs A and B, who had tested the hollandaise sauce and denied eating any other food served at the reception, and Chef C who had eaten a full serving of chicken and hollandaise sauce. SE was not isolated from the pool of 120 eggs taken from the hotel kitchen.

Six SE isolates from patients tested were phage type 8. SE, phage type 8, was also recovered from environmental samples of the henhouse where the eggs originated and from the ovaries of one of 60 necropsied hens from that henhouse.

Dose–response effects

Because the hollandaise sauce was prepared and thoroughly mixed in a single batch, creating a homogeneously contaminated vehicle, and because it was served to each person in measured 1-ounce portions, dose–response effects could be estimated. To control for variation in the amount of sauce absorbed by the chicken in different servings, we used consumption of both sauce and chicken to divide case-patients into three exposure groups. Those who ate all of the sauce, all of the chicken, or all of both items were the high-exposure group ($n = 109$). Those who ate most of the sauce, most of the chicken, or most of both items were the medium-exposure group ($n = 27$), and those who ate some of either or both items were the low-exposure group ($n = 29$).

Exposure group was inversely related to the time of onset of diarrhoea (Fig. 1). The median onset of diarrhoea occurred 17·5 h after the reception for the high-exposure group, 21 h after the reception for the medium-exposure group, and 37 h after the reception for the low-exposure group ($P = 0{\cdot}0006$).

The presence of certain symptoms varied with exposure group (Table 1). Patients in the high-exposure group were more likely than patients in the medium- or low-exposure groups to report body aches (94 *v.* 85 *v.* 71%, $P = 0{\cdot}001$) and vomiting (57 *v.* 56 *v.* 21%, $P = 0{\cdot}002$). A trend towards increased reporting of nausea with higher exposure group was also observed (84 *v.* 89 *v.* 52%, $P = 0{\cdot}001$). There was no observed dose–response effect for abdominal cramps, fever, or headache.

Follow-up survey questionnaires were completed and returned by 119 (70%) patients. Exposure group distribution was similar for all patients and for survey respondents: 65% of all patients and 66% of survey respondents were in the high-exposure group; 16% of all patients and 17% of survey respondents were in the medium-exposure group; 17% of all patients and 16% of survey respondents were in the low-exposure group. Exposure data were lacking for four (2%) patients and for one (1%) survey respondent.

Exposure group did not predict the likelihood of physician visits, stool culture, antimicrobial treatment, or hospitalization (Table 1). However, patients in the high-exposure group were more likely to have been treated with intravenous fluids than patients in the medium- or low-exposure groups (38 *v.* 35 *v.* 11%, $P = 0{\cdot}04$).

Among survey respondents, increased exposure was associated with increased median values for maximum 24-h stool frequency (20·0 *v.* 15·0 *v.* 12·5, $P = 0{\cdot}02$), acute weight loss in kilograms (5·0 *v.* 4·5 *v.* 3·2, $P = 0{\cdot}0001$), and the subjective severity of illness as rated from 1 (very mild) to 10 (worst imaginable)

Table 2. *Median values for clinical variables and illness duration by exposure group (survey respondents)**

Clinical variable	All respondents ($n = 119$)	Respondents by exposure group: High ($n = 79$)	Medium ($n = 20$)	Low ($n = 19$)	Jonckheere–Terpstra p value
Maximum 24-h stool frequency	19·0	20·0	15·0	12·5	0·02
Acute weight loss (kg)	4·5	5·0	4·5	3·2	0·0001
Severity of illness rating	9·0	9·5	8·0	7·0	0·0007
Highest recorded temperature (°C)	38·9	38·9	38·9	38·6	> 0·05
Illness duration					
No. days of diarrhoea	12·0	12·0	13·0	10·0	> 0·05
No. days of fever	3·0	3·0	3·0	2·5	> 0·05
No. days of normal activity lost	11·0	11·0	13·0	9·0	> 0·05
No. days of confinement to bed	6·0	6·5	6·5	3·0	0·04

* Non-responders excluded from the analysis.

(9·5 *v.* 8·0 *v.* 7·0, $P = 0·0007$). (Table 2). A dose–response trend that did not reach statistical significance was observed for maximum recorded temperature (38·9 *v.* 38·9 *v.* 38·6 °C, $P > 0·05$).

To evaluate the effect of ingested dose on illness duration, median values for the number of days of diarrhoea, fever, normal activity lost, and confinement to bed were compared for the three exposure groups. No clear dose–response effect was seen for the median number of days of diarrhoea, fever, or normal activity lost; however, the median number of days of confinement to bed increased with exposure (6·5 *v.* 6·5 *v.* 3·0, $P = 0·04$) (Table 2). Excluding persons > 60 years of age ($n = 15$) and those who were hospitalized for their illness ($n = 16$), the difference in median days of confinement to bed remained significant (6·0 *v.* 4·0 *v.* 3·5, $P = 0·03$), but other measures of illness duration did not show a dose–response effect. For all respondents, the mean number of days of confinement to bed was 6 (range 0–21), and the mean number of days of normal activity lost was 12·5 (range 0–27).

Stool carriage rates

Thirty-nine of 73 persons (53%) with SE isolated from an initial stool culture submitted follow-up stool samples. Samples were collected from 33 to 50 days after the reception and ⩾ 72 h after any antibiotic use. SE was isolated from 11 of 39 (28%) follow-up cultures. Follow-up cultures tended to yield salmonella more frequently with increasing exposure group (32% [8/25] *v.* 25% [2/8] *v.* 17% [1/6], $P = 0·3$), but this may have been due to chance. Persons who had been treated with ⩾ 3 days of antibiotic therapy were as likely to have SE isolated from a follow-up stool culture as those who had taken no antibiotics (31% [4/13] *v.* 32% [7/22]). All 11 repeat isolates and the three original isolates tested were susceptible to tested antimicrobials.

DISCUSSION

In the past decade, infections with *Salmonella enteritidis* have increased in North America and most European countries [10]. The outbreak described here was 1 of 68 SE outbreaks reported to CDC in 1990, when *S. enteritidis* was the most frequently reported *Salmonella* serotype in the United States [11]. Vehicles made from shell eggs have been implicated in the majority of foodborne SE outbreaks [7, 8, 11]. Gently heated foods prepared from pooled eggs, such as hollandaise and béarnaise sauces, are particularly likely vehicles. In this outbreak, the hollandaise sauce was implicated by several lines of evidence: it was prepared from pooled eggs at temperatures that do not kill salmonella; consuming it was strongly associated with illness among reception guests; it was the only food item from the reception eaten by two culture-positive foodhandlers; and SE isolated from the ovaries of a hen on the farm that produced the eggs used to make the sauce was the same phage type as the outbreak strain.

The hollandaise sauce was thoroughly mixed during preparation and was served in equal measured portions soon thereafter. Each portion was assumed to contain equal numbers of salmonella; relative, self-reported approximations of the amount consumed were used as a substitute for measured inoculum size. Significant dose–response trends were observed for incubation period, the presence of body aches and vomiting, maximum 24-h stool frequency and maximum weight loss, the subjective rating of illness severity, the likelihood of treatment with intravenous fluids and the duration of bedrest. The dose–response trend for maximum recorded temperature did not reach statistical significance in this study, which differs from the significant correlation between severity of illness and maximum recorded temperature recently reported in volunteers infected with *Shigella sonnei* [12]. This may be due to differences in the pathophysiology of salmonella and shigella infections or to less precise procedures for the collection of quantitative data used in this observational study.

In this outbreak, persons who reported eating only some of the sauce probably ate not less than one tenth of a portion. Although the overall difference in ingested inoculum for the three exposure groups may have been only 1 log, dose–response effects at this range are consistent with volunteer studies. Limited data from volunteer feeding studies suggest that for several non-typhoid *Salmonella* serotypes, rates of illness, hospitalization, and vomiting tend to increase even with small increases in dose [3–5]. For example, with *S. anatum* strain 1, rates of vomiting and hospitalization doubled among volunteers fed $8{\cdot}6 \times 10^5$ organisms compared with those fed $5{\cdot}9 \times 10^5$ organisms [3].

Our findings suggest that certain aspects of the pathogenesis of non-typhoidal salmonellosis are dose-dependent. Higher doses appear to provoke a more intense gastrointestinal response; the onset of diarrhoea occurs earlier, vomiting is more common and stool frequency is increased. This clinical picture engenders more profound dehydration and leads to greater weight loss and a greater need for intravenous fluid replacement. The systemic consequences of salmonellosis appear to be less dose-dependent; body aches may occur more commonly at higher doses, but abdominal cramps, headache, and fever are likely to be present at lower doses as well. Inoculum size was not a strong predictor of intensity nor duration of fever.

The duration of diarrhoea was also independent of dose; however, persons exposed to higher doses gave higher ratings to the severity of their illness and reported longer periods of bedrest before recovery.

The dose-related effects of acute salmonellosis underscore the importance of food protection measures designed to limit bacterial growth. Proposed USDA recommendations to refrigerate eggs during shipping and storage will not prevent contaminated eggs from reaching the marketplace or transmitting SE infection to consumers, but may decrease overall morbidity from these infections by reducing large-dose exposures related to eggs held at ambient temperatures [13].

These findings may have practical implications for future epidemiologic investigations of salmonellosis. In outbreaks where a higher proportion of cases present with body aches and upper gastrointestinal symptoms, investigators may choose to focus first on foods consumed within the previous 24 h. Conversely, when few cases have upper GI symptoms, longer incubation periods should be considered and food histories should include foods served 3–4 days before the onset of symptoms. Finally, these data illustrate how, in high-attack rate outbreaks where more than one food item is initially suspect, dose-response data may be used to implicate more precisely a particular vehicle.

This observational study has several limitations. Although the hollandaise sauce had not been epidemiologically implicated at the time the first questionnaire was administered, persons with more severe illness may have overreported hollandaise sauce consumption if they suspected it as the cause of the outbreak. Recall bias may also have affected reporting of symptoms, medical interventions and duration of illness among follow-up survey respondents. Because none of the hollandaise sauce was available at the time of the investigation, it was impossible to quantify the amount of salmonella it contained or to establish that contamination was truly homogeneous. Dose–response effects in this outbreak may have been enhanced by the properties of the vehicle; the high-fat content and semi-solid state would tend to protect salmonella from exposure to gastric acid, allowing a relatively high fraction of the ingested inoculum to reach the intestinal tract in a viable state [5, 14, 15].

Finally, the observed effects may be specific for the enteritidis serotype or even for this particular strain of SE. A recent report of associations between incubation period and severity of illness for infection with *S. typhimurium* suggest they may be more generalizable [6]. Similar epidemiologic investigations of outbreaks caused by other serotypes would help establish the reliability of these findings.

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