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The relationship between infecting dose and severity of disease in reported outbreaks of salmonella infections

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SUMMARY

The relationship between size of the infecting dose and severity of the resulting disease has been investigated for salmonella infections by reanalysis of data within epidemics for 32 outbreaks, and comparing data between outbreaks for 68 typhoid epidemics and 49 food-poisoning outbreaks due to salmonellas. Attack rate, incubation period, amount of infected food consumed and type of vehicle are used as proxy measures of infecting dose, while case fatality rates for typhoid and case hospitalization rates for food poisoning salmonellas were used to assess severity. Limitations of the data are discussed. Both unweighted and logit analysis models are used.

There is no evidence for a dose-severity relationship for *Salmonella typhi*, but evidence of a correlation between dose and severity is available from within-epidemic or between-epidemic analysis, or both, for *Salmonella typhimurium*, *S. enteritidis*, *S. infantis*, *S. newport*, and *S. thompson*. The presence of such a relationship affects the way in which control interventions should be assessed.

INTRODUCTION

In outbreaks of communicable disease it is commonly observed that many are exposed, a proportion become infected, some of these are ill and few die. While it is well established for many infections that the larger the infective dose or inoculum the greater the chance of being infected, the relation between infecting dose and severity of resulting illness is much less clear. This is mainly because it is usually impossible to measure individual infecting doses in human disease outbreaks. If there is a dose-effect, public health interventions can be expected to have a greater impact on severe than on total disease [1]. Knowledge of an effect is therefore important both for implementing and evaluating public health programmes. This study investigates the relation between infecting dose and severity of disease for salmonella outbreaks in man by comparative analysis of published data. Various proxy measures are used for dose and severity.

Direct evidence concerning the dose–severity relationship in man comes from the few volunteer experiments, chiefly carried out during research on typhoid vaccines. As the dose of *Salmonella typhi* increased so did the attack rate, while the median incubation period decreased [2]. The authors state that there was no

association between dose and severity of symptoms, but give no details. McCullough and Eisele [3–6] gave varying doses of several non-typhoid salmonellas to volunteers in experiments designed to test pathogenicity and to determine the minimal infective dose. As the dose increased, the proportion with positive faecal cultures and, at higher doses, with clinical disease both increased, but there were too few ill volunteers with each strain for any further conclusions on dose and severity to be drawn, and interpretation is complicated by the use of many volunteers for more than one feeding.

The only other direct evidence is from animal experiments. The interval from inoculation of mice with salmonellas to their death is negatively, linearly related to the logarithm of the dose of bacteria, at least for doses above the LD_{50}, the dose which kills half of those exposed [7–10], and a similar relationship is found in chicks [11]. Among mice, the case-fatality rate increases with dose [12]. It is difficult to study disease severity, short of death, using small animals, but in one study of chickens the duration of diarrhoea increased with salmonella dose [13]. For calves there appears to be an increase in severity with dose for several salmonella serotypes, but calves are expensive and the sample sizes very small [14–17].

For outbreak studies indirect measures are needed. The ingested dose is not known directly, but several proxy measures of relative dose are available. The most obvious is the amount of infected food consumed, but this is rarely recorded and the organisms are likely to be unevenly distributed in the food. Typhoid can be conveyed by food or water: it seems likely that the infecting dose in water-borne epidemics is lower [18]. In the volunteer experiments dose was related to attack rate and incubation period [2–6]. Where information on relative dose, attack rate and incubation is available in reports of natural outbreaks, the same associations can be found for both typhoid [19, 20] and the food-poisoning salmonellas [21].

Blaser and Newman [22] and Naylor [23] both suggest a negative correlation between attack rate and incubation period for several typhoid epidemics, which could be due to the common effects of dose, though variation in salmonella virulence between epidemics would give a similar result.

METHODS

In this meta-analysis of human salmonella outbreaks we have used four proxy measures of dose, amount of food, type of vehicle, attack rate and incubation period, in assessing whether dose influences severity of disease. Whilst various measures of severity are used for within-epidemic analysis, for comparisons of epidemics the case fatality rate is used for typhoid and hospitalization rate for other salmonellas, for reasons discussed below.

The criteria for selection of studies for re-analysis were as follows. Published reports were identified that gave data on severity and on a proxy measure of dose. They were found by searching the Bulletin of Hygiene, later Abstracts of Hygiene (from 1926), The Lancet (1920–45), The American Journal of Hygiene (1921–64), the British Local Government Board, Medical Officer's Report (later the Reports to the Local Government Board on Public Health and Medical Subjects and then

the Ministry of Health Reports on Public Health and Medical Subjects, from 1900), the National Communicable Diseases Center, later the Center for Disease Control Salmonella Surveillance Reports (1964–76) and the Morbidity and Mortality Weekly Reports (from 1976): any references from these journals, or from already identified articles, which it was thought might contain sufficient data were followed up. For the analysis of single epidemics, all identified reports that gave data on severity and on a proxy measure of dose were included. Where the data were anecdotal the reports are only mentioned briefly, as there is likely to be a bias towards inclusion of positive findings in a report.

For comparison between epidemics, the selection criteria for typhoid and for the other salmonellas differ because of the necessary use of different proxy measures of severity. Within the criteria, all located published outbreaks were included.

For typhoid, case fatality rate was chosen as an outcome measure which could be extracted from reports and could be compared between epidemics. As case fatality rates are much lower with antibiotic therapy, outbreaks occurring after 1945 were excluded. Common source typhoid epidemics were identified in the published literature and included in the study if they contained sufficient information on case fatality rate and attack rate or incubation period and involved at least eight cases. Outbreaks among hospital patients were excluded. As information on incubation period was scarce, post-war epidemics where the incubation period was given were also identified. They have only been included in the analysis when case fatality rate is not being considered.

Correlations were sought between: attack rate (AR) and incubation period; attack rate and case fatality rate (CFR); and incubation period and case fatality rate. For reasons addressed in the discussion the initial analysis was carried out unweighted (each epidemic carrying equal weight regardless of size). As an attempt to separate epidemics with more accurate information, a subgroup of pre-war epidemics was identified where the population exposed was well defined (such as guests at a reception, or people supplied with milk from one farm). For this subgroup weighted analysis was done using logistic regression. The models used were:

$$\text{Logit AR} = \text{Constant} + \beta(\text{Incubation}),$$

$$\text{Logit CFR} = \text{Constant} + \beta'(\text{Incubation}),$$

$$\text{Logit CFR} = \text{Constant} + \beta''(\text{AR}).$$

For the food poisoning salmonellas we have again used attack rates and incubation periods as measures of dose. Fatalities from non-typhoid salmonellas are unusual, and descriptions of cases are not detailed enough for any symptom-based measure of morbidity to be used. The only readily available measure of severity is the number of cases requiring hospitalization. Since this is obviously time- and culture-dependent we have only used epidemics reported in the National Communicable Disease Center (later Center for Disease Control) Salmonella Surveillance Reports. The hospitalization rate was taken as the proportion of cases who were hospitalized. Surveillance reports of common source outbreaks from the period 1964–74 were included if they contained sufficient information and involved more than eight people. Outbreaks involving hospital patients or mixed infections were excluded.

Correlations were sought between: attack rate and hospitalization rate; median incubation period and hospitalization rate; and attack rate and median incubation period. The analysis was carried out using unweighted linear regression and logistic regression. The models used for the logistic regression are:

$$\text{Logit hospitalization rate} = \text{constant} + \beta(\text{attack rate}),$$

$$\text{Logit hospitalization rate} = \text{constant} + \beta'(\text{incubation}).$$

RESULTS

Analyses of single epidemics

Amount of food

For typhoid only two reports allow comparison of amount of food with outcome. In an outbreak following a school picnic the case fatality rate was 3/17 for those who had whole portions of the affected ice cream and 0/6 for those with half portions ($P = 0{\cdot}5$ Fisher's 2-tailed test) [20]. The other report concerned a milk-borne outbreak involving 68 cases [24]. The author noted that among those who were ill, those who only took milk in their tea or coffee had very mild attacks.

For the food poisoning salmonellas we have found 11 reports which provide information on amount of food and severity. Mintz and colleagues [21] provide the most detailed breakdown of outcome by amount of food consumed, in an outbreak of 171 cases of *S. enteritidis* infection due to contaminated Hollandaise sauce. As the amount of sauce used increased, there were increases in the proportion of cases with body aches, nausea and vomiting, the maximum number of stools passed per 24 h, and acute weight loss, but not in duration of illness. Taylor [25] describes a small family outbreak of *S. typhimurium* in which the person who had eaten the most of the affected vehicle died. In five other reports, although it is stated that those who ate more had more severe disease, no supporting evidence is given [26–30].

Four reports failed to find an association. In an *S. typhimurium* outbreak affecting nearly 200 people, there were no differences in the mean maximum stool frequency or in the duration of illness for those who ate one or more pieces of the chicken vehicle [31]. However, the attack rate was not related to the number of pieces of chicken eaten either, so the bacteria may have been unevenly distributed. Two other negative reports refer to meat pies. In the first the pies were baked in two separate lots on different days, so uniform contamination is unlikely [32]. In the second, most of those who had severe disease had eaten the smaller pies but had kept them unrefrigerated for 24 h [33]. The last report refers to only six cases [34].

Four anecdotal reports suggest that food eaten later (after allowing time for bacteria to multiply) gave rise to more severe disease [28, 35–37].

Attack rate and outcome

In an extended water-borne typhoid outbreak in Bolton-upon-Dearne in 1921 attack rates and case fatality rates were reported by district, and showed no

particular pattern [38]. We have found no other studies of salmonella where attack rate and measures of severity are given by area.

Incubation period and outcome

In five reports of typhoid outbreaks individual incubation periods can be related to outcome [20, 39–42]. In some, including the two larger outbreaks [20, 39], the incubation periods for those who died were on average slightly shorter than for the others, but in none of the epidemics did the differences approach significance at the 5% level.

For the food poisoning salmonellas the picture is rather different. Of nine reports which give sufficient details, only one [43] failed to find an association between incubation period and severity. In an outbreak of *S. newport* food-poisoning in Sweden [44] information was available on 161 people; those with shorter incubation periods had more severe illnesses. In a large outbreak of *S. thompson* food-poisoning in Tennessee onset times were on average earlier in the 51 who were hospitalized than in 72 others [45]. Balice [26] describes a severe outbreak of *S. typhimurium* in Italy. All 83 people who ate the affected food became ill and there were five deaths. The mean incubation period overall was 21 h (range 8–30 h), and for the five who died it was 14 h. However, in an outbreak due to *S. newport* where information was available for 105 cases, it was noted that the median incubation period was 29 h overall, and 30 h for those with 'severe illness', defined by the number of different symptoms experienced. The number of cases in this group is not stated. It was also stated that there was no relationship between the length of the incubation period and the duration of illness [43]. The other five reports all suggest an association, but are based on small numbers of cases or have small numbers of deaths as their only outcome measure [32, 46–49].

Comparisons between epidemics: typhoid

Sixty-nine typhoid epidemics fulfilled the criteria, including eight post-war epidemics (see Appendix 1). Most were from Britain or the United States. Thirty-five were water-borne. Incubation periods were available for 27 epidemics, including 19 pre-1945 epidemics. The median incubation period was used whenever it was given. Attack rates were available for all but four of the epidemics.

The distributions of attack rates, incubation periods and case fatality rates are shown in Fig. 1. The association between them are shown in Figs 2 and 3. A log scale is used for the attack rate as the distribution of attack rates is skewed to the right. High attack rates were associated with short incubation periods but no significant correlations with case fatality rate were found.

Water-borne epidemics had longer incubation periods and lower attack rates. There was no difference in case fatality rates between water- and food-borne epidemics (Table 1). When the vehicle (water or food) was added to the regression equations, in a multiple regression model, the correlation between incubation period and attack rate was no longer significant, and the regression coefficient was reduced to −2·8 (95% confidence interval −6·1 to 0·5). There was still no association between case fatality rate and either attack rate or incubation period. The analysis was repeated for circumscribed pre-war epidemics where the

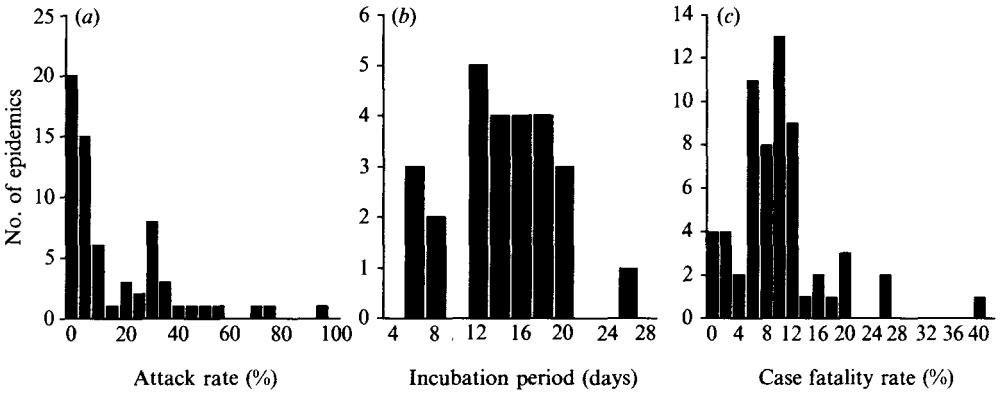

Fig. 1. Typhoid epidemics used in the comparison study. (*a*) Attack rates for 65 epidemics. (*b*) Incubation periods for 26 epidemics. (*c*) Case fatality rates for 61 pre-1945 epidemics.

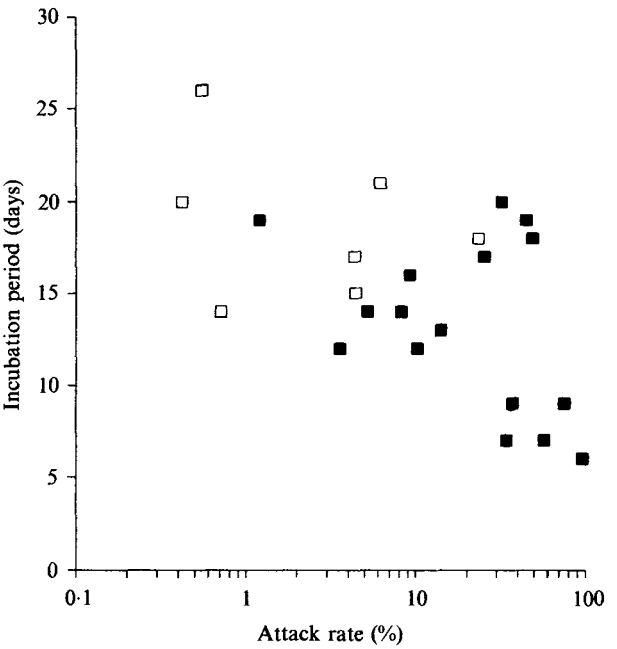

Fig. 2. The relationship between attack rate and incubation period for 23 typhoid epidemics. Each square represents an epidemic. □, water-borne: ■, food-borne. Correlation coefficient = −0.55 (95% confidence interval (CI) −0.78 to −0.17); regression coefficient = −4.01 (95% CI −6.64 to −1.38); constant = 18.92; $t = 2.99$; $p < 0.001$.

population exposed was well defined. Thirty-one epidemics fulfilled this criterion. No associations between incubation period, attack rate and case fatality rate where found in the unweighted analysis.

Logistic regression analysis for this subgroup of circumscribed epidemics showed a negative association between incubation and attack rate based on 11 epidemics which were all food-borne (likelihood ratio statistic (LRS) 93·2, one degree of freedom (D.F.), $P < 0{\cdot}001$, proportion of deviance explained = 15%).

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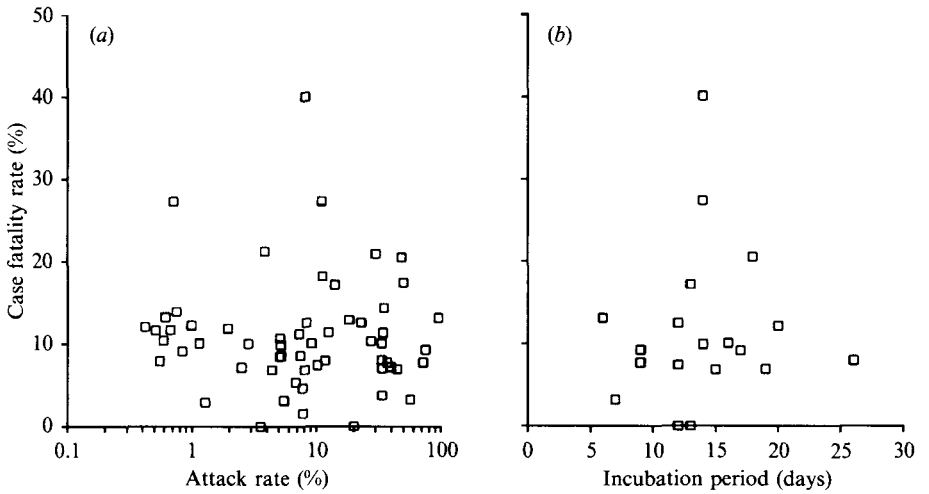

Fig. 3. The relationship between case fatality rate and (*a*) attack rate (for 58 pre-1945 typhoid epidemics) and (*b*) incubation period (for 19 pre-1945 typhoid epidemics). Each square represents an epidemic.

Table 1. *Comparisons between food and water-borne typhoid epidemics*

	No.	Mean	95% confidence interval	*P*	
Incubation period (days)					
Water-borne	8	18·5	(15·2–21·8)	0·007	(t test)
Food-borne	18	13·2	(11·0–15·4)		
Attack rate (%)*					
Water-borne	34	3·8	(2·3–6·3)	< 0·001	(t test)
Food-borne	28	16·7	(10·8–25·9)		
Case fatality rate (%)†					
Water-borne	32	10·3	(8·4–12·2)	0·8	(Kruskal–Wallis)
Food-borne	26	11·4	(8·0–14·9)		

* Geometric mean given.
† Pre-1945 epidemics only.

Incubation period showed a just significant positive association with case fatality rate based on 13 epidemics (LRS 4·4, 1 D.F., $P = 0·04$). There was no association between attack rate and case fatality rate.

There was a non-significant negative correlation between case fatality rate and the date of the epidemic. When the year of the outbreak was included in multiple regression or logistic regression models between case fatality rate and incubation period or attack rate the regression coefficients hardly changed.

Comparisons between epidemics: food-poisoning salmonellas

Sufficient numbers of suitable reports were available for analysis for four different salmonellas: *S. typhimurium*, *S. enteritidis*, *S. thompson*, *S. infantis*. Details of the epidemics are given in Appendix 2. All except one epidemic (of *S. typhimurium*) were food-borne.

Plots of hospitalization rates by attack rates are shown in Fig. 4. The results of fitting the logistic regression model are given in Table 2.

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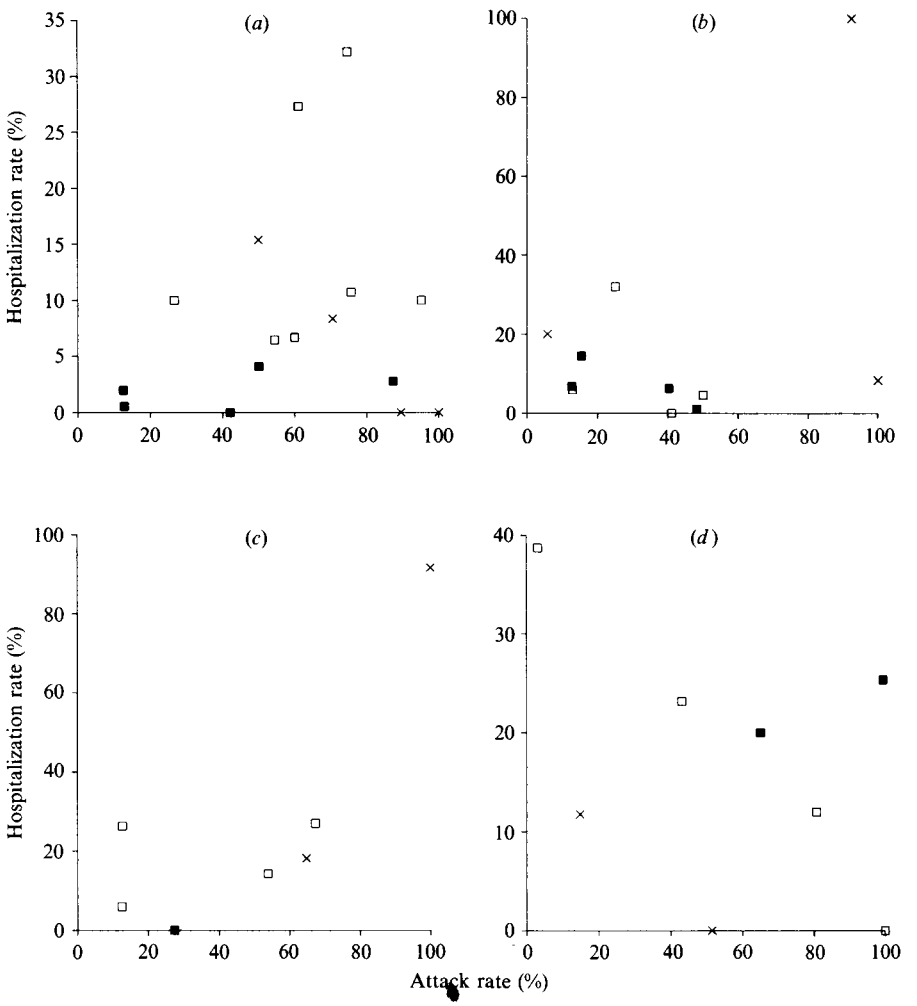

Fig. 4. The relationship between hospitalization rate and attack rate for four food-poisoning salmonellas. Each square represents an epidemic. ×, Epidemics of less than 20 cases; □, epidemics of 20–100 cases; ■, epidemics of over 100 cases (*a*) *S. typhimurium* (16 epidemics); (*b*) *S. enteritidis* (11 epidemics); (*c*) *S. infantis* (7 epidemics); (*d*) *S. thompson* (8 epidemics).

S. typhimurium. Information was available for 16 epidemics. Linear regression showed no relationship between attack rate and hospitalization rate but logistic regression showed a positive correlation, giving the model:

$$\text{Logit HR} = -5{\cdot}6 + 0{\cdot}0406\ (\text{AR}),$$

where HR is hospitalization rate and AR is attack rate. When the one large water-borne epidemic was excluded, the coefficient decreased to 0·0201 (S.E. 0·0058) but the model remained highly significant: LRS = 12·5, 1 D.F., $P < 0{\cdot}001$.

S. enteritidis. The linear regression, based on 11 epidemics, did not show a significant association, but again logistic regression showed a positive correlation, giving the model:

$$\text{Logit HR} = -3{\cdot}5 + 0{\cdot}0223\ (\text{AR}).$$

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Table 2. *The association between hospitalization rate and attack rate for salmonellas: logistic regression results*

Serotype	Coefficient	Standard error	Constant	LRS*	D.F.†	*P*	Deviance explained (%)
typhimurium	0·0406	0·0028	−5·6	135	1	< 0·001	58·7
enteritidis	0·0223	0·0063	−3·5	11·8	1	< 0·001	10·7
infantis	0·0415	0·0072	−3·6	37·2	1	< 0·001	43·6
thompson	−0·0069	0·0043	−0·96	2·5	1	0·1	

* Likelihood ratio statistic.
† Degrees of freedom.

After excluding the one outlying epidemic with a high hospitalization rate (Fig. 4) the association was lost.

S. infantis. The linear regression model, based on seven epidemics, was just significant, but is influenced by a small epidemic with high attack and hospitalization rates. (Correlation coefficient = 0·75, regression coefficient = 0·71 (95% confidence interval 0·16–1·25), constant = −7·96, $t = 2·55$, $P = 0·05$). Logistic regression also showed a positive correlation, giving the model:

$$\text{Logit HR} = -3·6 + 0·0415\ (\text{AR}).$$

After excluding the small epidemic with the high attack and hospitalization rates, the coefficient in the logistic regression model decreased to 0·0237 (S.E. 0·0094) and the strength of the association was reduced, but it remained significant (LRS = 6·2, 1 D.F., $P = 0·01$).

S. thompson. The scatter plot (based on eight epidemics) shows no trend in the results, and neither linear nor logistic regression models had coefficients which were significantly different from zero.

Incubation periods were only available for a few epidemics of each serotype. For *S. typhimurium*, six epidemics contained information on both incubation and hospitalization rate: no association was found using linear or logistic regression. Even less information was available for the other serotypes.

DISCUSSION

For typhoid the results confirm the suspected relationship between incubation period and attack rate. Since there is no evidence that more virulent forms of typhoid are found in food than in water, the long incubation periods and low attack rates found in water-borne epidemics suggest that the dose in these epidemics is, on average, smaller. By contrast, correlations between attack rate or incubation period and case fatality rates were not found (with one exception), even though both dose effects and any differences in virulence would be expected to lead to such correlations.

There are, however, limitations to the typhoid data. The attack rate depends on both full ascertainment of cases and correct ascertainment of those at risk, here taken as those exposed during the epidemic. Immune status was usually unknown. The most accurate estimates of those exposed are those obtained from circumscribed epidemics occurring after specific meals or at a camp where everyone can be traced and those who consumed a particular food or drank the

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water can be identified. Milk-borne epidemics where the numbers of people on the milk round is known give reasonable figures. When the domestic water supply is the source, the number of people using the supply is only an approximate estimate, and those who avoid being truly exposed by buying or boiling their drinking water is unknown. Also, it is unlikely that the whole of the supply is significantly contaminated. Full ascertainment of cases is also difficult, but again it is likely to be most complete for the most circumscribed epidemics where individuals are actively traced. Large epidemics rely on notification of cases which will be incomplete.

The incubation period can be estimated only for point source epidemics and then only if dates of onset of illness rather than dates of notification are available. Late cases may be missed and secondary cases may be mistakenly included (leading to under- and over-estimates of the median incubation period respectively). The median incubation has been used as the epidemic curve is approximately log-normal, and it is usually the measure quoted. For a few epidemics where only the mode or 'average' was given, that was used instead; they are usually similar (see Appendix 1).

Identification of deaths from typhoid is probably more complete than identification of cases, leading to overestimation of the case fatality rate, to an extent which will vary from epidemic to epidemic, depending on the completeness of case ascertainment. It is a crude measure of severity, particularly as the numbers are small in some of the epidemics, and unmeasureable factors associated with the place of the outbreak would be expected to influence how many die.

Too few of the epidemics give sufficient information on the age, sex, or immune status of the people involved for these variables to be taken into account. The year of the epidemic may be expected to be associated with the case fatality rate, but would only be associated with incubation period or attack rate if methods of investigating or reporting outbreaks changed. Controlling for the year of the epidemic did not affect the results in the multiple regression analyses.

Epidemics could only be included in the study if they contained sufficient information. All identified epidemics which fulfilled the criteria were included, but they are not necessarily representative of all typhoid epidemics.

Although some of the data problems will lead to non-differential misclassification (and therefore to underestimation of associations) certain directions of bias appear likely: attack rates are likely to be unduly low in water-borne outbreaks due to both underestimation of cases and overestimation of susceptibles, and case fatality rates will be disproportionately high in epidemics with poor case ascertainment, which include most of the water-borne epidemics. It was felt that the large epidemics were often more inaccurate and more likely to be biased than the smaller epidemics so calculations are presented both weighted and unweighted.

Turning to the data, the finding of the expected correlation between attack rate and incubation period suggests that the data are not so crude as to be useless. Similarly, for water-borne epidemics, although the low attack rates may be due to bias, the longer incubation periods are unlikely to be, and the finding fits with the expected low dose of organisms in water.

The case fatality rates were the same in water as in food-borne epidemics. This could be true, reflecting no dose-effect, or could be due to bias giving falsely high

case fatality rates in water-borne outbreaks. Attack rates did not predict case fatality rates. This could be true or could reflect the falsely low attack rates and high case fatality rates of less well investigated outbreaks. No association was found when consideration was restricted to circumscribed outbreaks. Incubation period did not predict case fatality rate in most of the analyses. Again, although this may be true both variables, and particularly case fatality rate, are subject to considerable error in measurement. The weighted analysis of the circumscribed epidemics produced a surprising positive correlation between incubation period and case fatality rate. This was only just significant.

Overall, the comparison of data between typhoid epidemics provides no evidence of an association between dose (as measured by incubation period, attack rate or vehicle) and severity (as measured by the case fatality rate). While the data are too crude for an association to be excluded, this finding contrasts with the outbreaks due to other salmonellas but fits with the conclusions from Hornick's volunteer studies [2].

The results from food-poisoning salmonellas provide evidence of a correlation between attack rates and case-hospitalization rates. The evidence for incubation period was too rudimentary to be useful.

For the non-typhoid salmonellas the unweighted linear regression models are too simplistic as the epidemics range in size from 10 cases to several hundred (and to 14000 in the one water-borne epidemic – see Appendix 2). Unlike the typhoid data, and with the possible exception of the water-borne epidemic, there is no reason to believe that the figures in the larger epidemics are any less accurate than those in the smaller epidemics, so it seems appropriate to weight the epidemics according to size. The logistic regression model has the added advantage that it does not require the variables to be normally distributed, which is more appropriate given the small numbers involved. For three of the serotypes of salmonella the coefficients were highly significantly different from zero, and for *S. typhimurium* and *S. infantis* around 50% of the deviance in the results was explained by the model.

The epidemics studied here are not necessarily representative of all epidemics in the USA as not all are reported, and only the reports containing sufficient information could be included. Although all of the epidemics came from one country over a short period, criteria for hospitalization may have varied between epidemics, probably leading to under-estimation of any correlation. However, the hospitalization threshold may be higher in a large epidemic, which would bias the results in the weighted analyses. Lack of data prevented controlling for age, though those at the extremes of age are more likely to be hospitalized and may also have different attack rates.

The results for food poisoning salmonellas point to a positive correlation between attack rate and hospitalization rate at least for some types of salmonella. This is consistent with a dose effect whereby higher doses give higher attack rates and more severe disease, though differing virulence between different strains would give similar results. The results from the single epidemics tend to support the dose–severity correlation, though within an epidemic a correlation between incubation period and severity could be due to individual differences in susceptibility as well as dose.

Overall, therefore, for typhoid, there is no evidence of a dose–severity relationship. Attack rate and incubation period are both related to dose, but there is no evidence that they are in turn related to severity. The results for the other salmonellas are very different. The evidence as a whole, from individual epidemics and from the comparison of hospitalization rates, suggests that there is a dose–severity relationship at least for *S. enteritidis*, *S. typhimurium*, *S. infantis*, *S. newport* and *S. thompson*.

This contrast is reflected in the differing response to challenge of subjects who are partially immune. In volunteer experiments with typhoid, vaccines gave protection against low but not high challenge doses, but once clinical disease occurred the severity of the disease and the number of relapses were not altered by vaccination [2, 105]. This is consistent with dose influencing only the proportion of people becoming ill and not the severity of the infection. However, for the food-poisoning salmonellas, when subjects who had become ill were rechallenged, if they became ill again the severity of the illness was usually less than that of the initial illness, despite higher challenge doses being used [4]. This change in severity with immunity is consistent with a dose–severity relationship.

Knowledge of whether a dose–severity relationship exists is important in public health. If there is a relationship, then interventions such as improvements in sanitation, which can be expected to lower the dose, could have a greater impact on the number of severe cases than on the total number of cases [1], and in evaluation of such interventions it would be important to assess numbers of severe cases as well as changes in case incidence. Where there is no dose–severity relationship, or where it is unimportant compared to other determinants of variation in severity between individuals, the case incidence would suffice for assessment.

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Appendix 1. *Typhoid epidemics*

Ref.	Year	Place	Vehicle	Incubation median (days)	Attack rate % (no.)	Case fatality rate % (no.)
50	1881	Blackburn	Water		0·61 (?/?20000)	13·19 (24/182)
51	1885	Pennsylvania	Water		12·55 (1004/8000)	11·35 (114/1004)
50	1893	Worthing	Water		8·33 (1298/15579)	12·48 (162/1298)
50	1893	Worthing	Water		3·87 (113/2919)	21·24 (24/113)
52	1897	Maidstone	Water		8·08 (?/?20000)	6·81 (132/1938)
41	1902	Winchester	Oysters*	14	8·20 (10/122)	40·00 (4/10)
41	1902	Southampton	Oysters*	16	9·17 (10/109)	10·00 (1/10)
53	1904	Brislington	? Carrier*		72·22 (26/36)	7·69 (2/26)
50	1904	Lincoln	Water		1·95 (1058/54204)	11·81 (125/1058)
54	1908	Minnesota	Water	15	4·40 (440/10000)	6·82 (30/440)
55	1909	Conway	Milk*		11·11 (26/234)	18·18 (10/55)
56	1910	Oakenshaw	Milk*		11·78 (53/450)	7·94 (5/63)
57	1911	Iowa	Water		2·83 (170/6000)	10·00 (17/170)
58	1912	Strood, Kent	Water		0·51 (69/13428)	11·59 (8/69)
59	1912	Ringwood, Hants	Water*		50·00 (23/46)	17·39 (4/23)
60	1912	Colne	Milk*		7·44 (67/900)	8·57 (6/70)
61	1912	Rockford, Ill.	Water	20	0·42 (199/47500)	12·06 (24/199)
40	1912	Iowa	Water	14	0·71 (11/1550)	27·27 (3/11)
62	1912	Texas	Milk*		1·28 (25/1950)	2·94 (1/34)
63	1913	Kenilworth	Water		0·84 (44/5258)	9·09 (4/44)
64	1913	Quincy, Ill.	Water	26	0·55 (202/37000)	7·92 (16/202)
65	1914	Hanford, CA	Spaghetti*	7	56·67 (85/150)	3·23 (3/93)
66	1915	Colusa, CA	Milk*	12	3·58 (23/643)	0·00 (0/23)

Appendix 1. (*cont.*)

Ref.	Year	Place	Vehicle	Incubation median (days)	Attack rate % (no.)	Case fatality rate % (no.)
20	1916	Helm, CA	Icecream*	6	95·83 (23/24)	13·04 (3/23)
67	1917	California	Water		20·00 (52/260)	0·00 (0/52)
68	1920	Salem, Ohio	Water		7·85 (785/10000)	1·53 (12/785)
38	1921	Bolton-Dearne	Water		0·67 (137/20497)	11·68 (16/137)
38	1921	Bolton-Dearne	Water		7·26 (260/3581)	11·15 (29/260)
69	1924	Chicago	Oysters	12		12·40 (16/129)
75	1924	Tennessee	Milk*		33·33 (100/300)	8·00 (8/100)
70	1925	Michigan	Food*	13	14·00 (35/250)	17·14 (6/35)
72	1925	Japan	? Food*	18	48·68 (37/76)	20·45 (9/44)
51	1926	Hanover	Water		0·59 (2500/425000)	10·40 (260/2500)
51	1927	Montreal	Milk		5·10 (3601/70576)	10·66 (533/5002)
73	1928	Royal Navy	Lettuce*	12†	10·22 (95/930)	7·37 (7/95)
74	1928	New York State	Water		1·15 (248/21599)	10·08 (25/248)
75	1929	Rio de Janeiro	Water*		18·31 (39/213)	12·82 (5/39)
76	1929	Massachusetts	Chicken*	19	44·62 (29/65)	6·90 (2/29)
77	1931	Porto Rica	Water*		33·33 (10/30)	10·00 (1/10)
78	1932	Denby Dale	Water		5·07 (71/1400)	8·45 (6/71)
79	1932	Genoa	Water		2·51 (42/1672)	7·14 (3/42)
80	1932	N Spain	Water		7·79 (87/1117)	4·60 (4/87)
81	1932	Massachusetts	Milk*		39·68 (25/63)	7·14 (2/28)
82	1932	Dumfriesshire	Water		5·50	3·13 (2/64)
83	1933	Malton, Yorks	Water		5·22 (235/4500)	8·52 (23/270)
84	1933	New South Wales	Food*		11·00 (33/300)	27·27 (9/33)
85	1934	Black Forest	Water*	17		9·09 (3/33)
86	1935	Lourdes	?		6·82 (75/1100)	5·33 (4/75)
87	1935	Philadelphia	Salad*		33·77 (77/228)	6·98 (6/86)
88	1936	England	?*		35·00 (14/40)	14·28 (2/14)
89	1936	Bournemouth	Milk	14‡	5·18 (518/10000)	9·85 (51/518)
90	1936	Mittelbaden	Icecream*	13		0·00 (0/24)
91	1936	Massachusetts	Salad*	9	37·14 (13/35)	7·69 (1/13)
92	1937	Croydon	Water		0·75 (?/?42000)	13·87 (43/310)
93	1937	Kentucky	Water*		22·86 (16/70)	12·50 (2/16)
94	1938	S. Africa	Milk*		30·06 (52/173)	20·90 (14/67)
95	1939	Louisiana	Oysters*	9	75·00 (87/116)	9·20 (8/87)
24	1942	Canada	Milk*		27·50 (66/240)	10·29 (7/68)
96	1943	Switzerland	Water*		33·75 (27/80)	3·70 (1/27)
97	1943	Malta	Water		0·99 (1275/)	12·20 (156/1275)
98	1944	Middle East	? Food*		34·35 (79/230)	11·25 (9/80)
99	1950	Egypt RAF Unit	Mock cream	7†	34·06 (234/687)	0·0 (0/234)
100	1958	Monark	Water	21	6·18 (34/550)	2·94 (1/34)
101	1961	Louisiana	Chicken	20	32·00 (31/97)	0·00 (0/31)
19	1963	Zermatt	Water	17	4·37 (437/10000)	0·69 (3/437)
102	1969	Audrain, USA	Water	18†	23·36 (25/107)	0·00 (0/25)
103	1971	Trinidad	Icecream	19	1·20	0·00
104	1971	Pennsylvania	? Food	17	25·38 (33/130)	6·06 (2/33)

* Circumscribed pre-1945 outbreaks (see text).
† Modal incubation period.
‡ 'Average' incubation period.

Appendix 2. *Salmonella epidemics from CDC Salmonella Surveillance*

Ref.*	Place	Date	Vehicle	Attack rate % (no.)	Hospital rate % (no.)	Incubation median (hours)
S. typhimurium						
30:8	New Jersey	1964	Wedding	14·9 (35/235)		15
33:4	Michigan	1964	Icecream	81·8 (9/11)		19
38:2	California	1965	Water	12·7 (14000/110000)	0·5 (75)	

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Appendix 2. (*cont.*)

Ref.	Year	Place	Vehicle	Incubation median (days)	Attack rate % (no.)	Case fatality rate % (no.)
43:7	1965	N. Carolina	Potato salad	50·0 (244/488)	4·1 (10)	96
59:4	1966	Montana	Turkey	54·4 (31/57)	6·5 (2)	48†
63:5	1967	Tennessee	Potato salad	35·7 (215/602)		32
77:2	1968	N. Carolina	Icecream	89·5 (17/19)	0·0 (0)	
77:4	1968	New Jersey	Cafe	42·0 (245/583)	0·0 (0)	21‡
83:2	1969	New York	Spaghetti	50·0 (13/26)	15·4 (2)	34‡
102:2	1970	N. Carolina	Barbecued ham	74·7 (56/75)	32·1 (18)	
104:2	1970	Missouri	Icecream	100·0 (11/11)	0·0 (0)	
105:1§	1970	Tennessee	Barbecued pork	95·2 (40/42)	10·0 (4)	24‡
105:1§	1970	Tennessee	Barbecue	70·6 (12/17)	8·3 (1)	30
105:1§	1970	Tennessee	Turkey	87·3 (144/165)	2·8 (4)	
110:2	1971	Michigan	Smoked fish	75·7 (28/37)	10·7 (3)	
112:2	1971	New Jersey	Roast beef	61·1 (22/36)	27·3 (6)	
115:2	1972	New Jersey	Bakery cakes	12·5 (150/1200)	2·0 (3)	
118:2	1972	Wisconsin	Hamburger?	26·7 (20/75)	10·0 (2)	
116:3	1972	Virginia	Icecream	60·0 (45/75)	6·7 (3)	
S. entertidis						
38:5	1965	New Jersey		50·0 (65/130)	4·6 (3)	
77:4	1968	Ohio	Icecream	100·0 (12/12)	8·3 (1)	
93:2	1969	Alaska	Whale	95·9 (93/97)		9
99:5	1970	Columbia	Picnic	48·1 (181/376)	1·1 (2)	28‡
101:4	1970	Pennsylvania	Salad	(130/)	23·1 (30)	18
102:2	1970	Florida	? Turkey	15·4 (139/900)	14·4 (2)	
103:2	1970	Michigan	Prison cafe	40·3 (353/876)	6·2 (22)	
104:2	1970	Georgia	Icecream	92·3 (12/13)	100·0 (12)	
104:2	1970	Nebraska	Roast meat	12·6 (252/2000)	6·8 (17)	
116:2	1972	California	Ham?	41·0 (41/100)	0·0 (0)	
116:2	1972	Rhode Island		5·8 (10/172)	20·0 (2)	
117:2	1972	Oregon		12·9 (17/132)	5·9 (1)	
123:2	1974	Indiana	Icecream	25·0 (25/100)	32·0 (8)	
S. infantis						
71:5	1968	Kentucky	Ham	67·3 (37/55)	27·0 (10)	20
85:2	1969	Tennessee	Smoked turkey	64·7 (11/17)	18·2 (2)	29‡
85:3	1969	Texas	Turkey	53·9 (28/52)	14·3 (4)	11
116:3	1972	Kansas	Icecream	100·0 (12/12)	91·7 (11)	
117:2	1972	Illinois	Bread dressing	12·7 (38/300)	26·3 (10)	
120:2	1973	Oregon	Roast beef	27·3 (123/450)	0·0 (0)	
123:2	1974	Texas		12·5 (50/400)	6·0 (3)	
S. thompson						
44:3	1965	St Louis	Icecream	92·3 (12/13)		18
95:2	1969	New Orleans	Church supper	99·5 (200/201)	25·4 (18)¶	13‡
99:1	1970	Tennessee	Barbecued pork	(303/)	17·8 (54)	54
102:2	1970	New Jersey		65·0 (130/200)	20·0 (26)	
112:2	1971	Maine	Chicken salad	51·5 (17/33)	0·0 (0)	29‡
113:2	1971	Iowa	Restaurant	43·2 (95/220)	23·2 (22)	
116:3	1972	Pennsylvania	Coconut cream	3·1 (31/1000)	38·7 (12)	
119:2	1973	Florida	Inflight food	14·8 (17/115)	11·8 (2)	
120:2	1973	Los Angeles	Custard pie	100·0 (23/23)	0·0 (0)	
120:2	1973	Pennsylvania	Roast beef	80·7 (25/31)	12·0 (3)	

* References give issue and page no.
† Incubation is 'average'.
‡ Incubation is mean.
§ Same restaurant.
¶ Information for 71 cases only.

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