4 Hazard Characterization

INTRODUCTION

Hazard characterization describes adverse effects resulting from ingesting a microorganism. It also gives a dose-response relationship, provided data are obtainable.[1] Information on the adverse effects of *Salmonella* Enteritidis (SE) and other non-typhoid *Salmonella* are considered in chapter 2. A dose-response model describes the probability of a specific response in a specific population as a function of dose. The biological basis for dose-response models results from interactions among pathogen, host, and food matrix (Figure 4-1). Infection and illness result from the pathogen successfully passing multiple barriers in the host. Each individual pathogen has some particular probability of overcoming a barrier, which is conditional on the previous step(s) being completed successfully.[1]

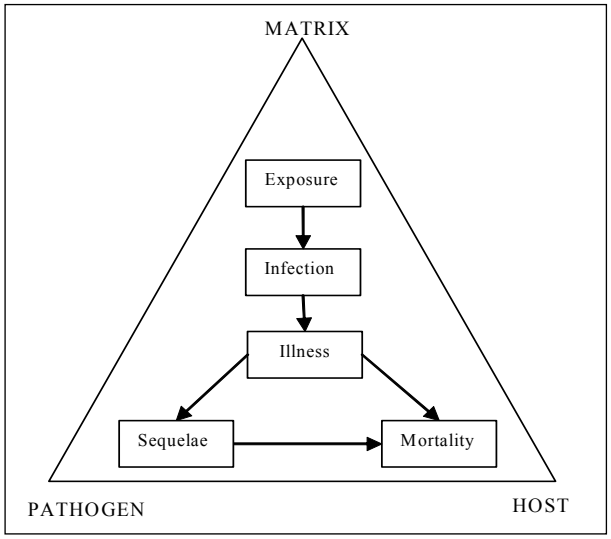

FIGURE 4-1 HAZARD CHARACTERIZATION TRIANGLE.[2]

This chapter presents data available to model a dose-response relationship for *Salmonella* spp., together with the beta-Poisson model produced by the Joint Expert Meetings on Microbiological Risk Assessment (JEMRA). The strengths and weakness of the JEMRA model are discussed along with reasons for selecting the JEMRA model for use in this risk assessment. This chapter refers extensively to the Joint FAO/WHO Risk Assessment of *Salmonella* spp. in Eggs and Broiler Chickens, a draft of which can be found in Annex I. This chapter also provides an estimate of yearly cases of illness, hospitalization, sequellae, and death from SE in eggs in the U.S. These estimates were derived from public health surveillance systems, and they provide a benchmark for comparing the results of a probabilistic model.

Joint Expert Meetings on Microbiological Risk Assessment (JEMRA)

JEMRA is a joint FAO/WHO expert group organized to conduct risk assessments on microbiological hazards in foods. JEMRA generally conducts risk assessments in response to requests from the Codex Committee on Food Hygiene (CCFH). A small international group of risk analysts drafts the assessment over a two-year period. The drafts are reviewed during weeklong consultations that occur twice during the two-year process. The final report is peer reviewed. Currently, JEMRA has completed a risk assessment on *Salmonella* spp. in broilers and eggs and has several other risk assessments in process.

DATA SOURCES

Generic Data Sources

A Joint FAO/WHO Consultation on Hazard Characterization identified several generic sources of data that may be useful in developing a mathematical relationship between dose and response.[1] Each of these sources contributes in varying degrees to an understanding of the pathogen host food-matrix interactions that influence the potential public health risks attributable to a disease agent. An assessment of the strengths and limitations of various data sources is critical to selecting appropriate data for use in this risk assessment.[1]

The relevance of data from the sources in Table 4-1 can be difficult to judge. However, in general, human data are preferred to animal data, which in turn are preferable to *in vitro* data. Data on the pathogen of concern are preferred to data on surrogate organisms, which should only be used on the basis of solid biological evidence such as common virulence factors.[1] The data from each of these sources that was considered most relevant for this risk assessment are summarized in the sections that follow.

Dose-response Data

One source of data available for calculating a dose response relationship is information collected during investigations of foodborne illness outbreaks. Table 4-1 summarizes the strengths and weaknesses of these kinds of data. The Joint Expert Group collected data from countries

worldwide and identified 20 outbreaks that included sufficient information on dose and attack rate to develop a dose-response model (Table 4-2).

TABLE 4-1 EVALUATION OF OUTBREAK DATA FOR DEVELOPING A DOSE-RESPONSE MODEL.

Pros	• Data from low dose exposures are available. • Exposed population more closely resembles the population at risk; therefore, these results may be easier to generalize to the population under consideration. • The strains and serotypes included are ones implicated in foodborne human illness. • Data reflect a range of food chemistries associated with transmission.
Cons	• Measurements of concentration of bacteria in food can be misleading because of the non-homogenous nature of pathogens in food commodities. • The quantity of food consumed is often not recorded. Consequently, an estimate of the food consumed or average serving size is often used to calculate dose. • It can be difficult to assess accurately the exposed population as well as the number of ill people because of underreporting. • Information on age, immunologic health, and underlying debilitating disease or stress factors of patients is often not available, making it difficult to differentiate susceptible subpopulations that are more susceptible.

TABLE 4-2 *SALMONELLA* OUTBREAKS USED IN DEVELOPING THE JEMRA DOSE-RESPONSE RELATIONSHIP.

Otbrk Ref #	Serotype	Country	Log_{10} Dose (Uncertainty) Min	Log_{10} Dose (Uncertainty) Max	Attack Rate (Uncertainty) Min	Attack Rate (Uncertainty) Max
1	*S.* Typhimurium	US	1.57	2.57	11.20%	12.36%
2	*S.* Heidelberg	US	1.48	2.48	28.29%	36.10%
3	*S.* Cubana	US	4.18	4.78	60.00%	85.71%
4	*S.* Infantis	US	6.06	6.66	100.00%	100.00%
5	*S.* Typhimurium	US	3.05	4.05	52.36%	57.64%
7	*S.* Newport	US	0.60	1.48	0.54%	2.59%
11	*S.* Enteritidis	US	4.00	5.00	100.00%	100.00%
12	*S.* Enteritidis	US	1.00	2.37	6.42%	7.64%
13	*S.* Typhimurium	US	8.00	8.88	100.00%	100.00%
18	*S.* Enteritidis	Japan	5.13	5.57	60.00%	60.00%
19	*S.* Enteritidis	Japan	6.03	6.48	87.70%	100.00%
20	*S.* Enteritidis	Japan	2.69	3.14	18.61%	36.41%
22	*S.* Enteritidis	Japan	6.02	6.47	52.17%	61.32%
23	*S.* Enteritidis	Japan	5.53	5.97	84.62%	84.62%
24	*S.* Enteritidis	Japan	1.45	1.89	12.19%	23.96%
25	*S.* Enteritidis	Japan	3.36	3.80	39.85%	39.85%
30	*S.* Enteritidis	Japan	3.53	3.97	60.14%	70.90%
31	*S.* Enteritidis	Japan	2.37	2.82	25.62%	30.04%
32	*S.* Enteritidis	Japan	1.11	1.57	26.92%	26.92%
33	*S.* Oranienburg	Japan	9.63	10.07	100.00%	100.00%

Source: FAO/WHO.[2]

Generic Data Sources for Dose-Response (WHO/FAO Expert Consultation in Bilthoven, 1990)

Human illness outbreaks—An epidemiological investigation is sometimes undertaken to identify the cause of a foodborne illness outbreak, limit its further spread, and provide recommendations on preventing the problem in the future. These data can serve as a means for deriving dose-response relations and for evaluating the plausibility of risk assessments.

Volunteer feeding trials—Dose-response relationships for pathogenic microorganisms have been derived from studies where humans were exposed to the agent under controlled conditions. Feeding studies using volunteers have been carried out for a limited number of pathogens. Most of these studies were conducted in conjunction with vaccine trials.

Biomarkers—Biomarkers are measurements of host characteristics that indicate exposure of a population to a hazard or the extent of adverse effect caused by the hazard. They are generally minimally invasive techniques that were developed to assess the status of the host.

Animal studies—Animal studies overcome many of the logistical and ethical limitations associated with human volunteer feeding studies. Large varieties of different animal models have been used to understand the pathogen, host, and matrix factors and develop dose-response relationships.

Expert elicitation—Expert elicitation is a formal approach to the acquisition and use of expert opinions, in the absence of, or to augment available data.

In vitro studies—The use of cell, tissue, or organ cultures and related biological samples has been used to characterize the effect of a pathogen on a host. These studies are of greatest use in qualitative characterizations of pathogen virulence, but they may also be used to evaluate the effects of defined factors on the disease process.

Intervention studies—Human trials where the impact of a hazard is evaluated by reducing exposure for a defined sample of a population. The incidence of disease or a related biomarker is then compared to a control population to assess the magnitude of the response differential for the two levels of exposure.

A second source of data on dose and response for *Salmonella* spp. is human feeding trial studies.[3-5] Some strengths and weaknesses of these kinds of data are presented in Table 4-3. These data were collected by dosing healthy male prisoners with a defined number of organisms in a liquid medium. The pathogen levels used were high relative to the levels generally observed in foodborne illness outbreaks.

In general, the variables of interest in human feeding study data are well controlled but less representative of real-world situations. For example, the number of organisms given to human volunteers in feeding trials is known with great accuracy, but those numbers are generally much higher than people are exposed to in reported foodborne illness outbreaks. On the other hand, data from outbreak investigations are very representative of the exposure levels and the diversity in response likely to occur in human populations. However, in outbreak studies, the variables of interest are measured after the outbreak occurred; consequently, the uncertainty in the measurement is high.

A beta-Poisson model fit to naïve human feeding trial data greatly underestimates the probability of illness as observed in the outbreak data (Figure 4-2). Consequently, the Joint Expert Group chose to use only the outbreak dataset in developing a dose-response relationship. Similarly, accurate representation of the exposure levels and the variation in human responses to foodborne pathogens is more important than the precision provided by the human feeding trial studies in developing a dose-response relationship for this risk assessment.

TABLE 4-3 EVALUATION OF HUMAN FEEDING TRIAL DATA FOR DEVELOPING A DOSE-RESPONSE RELATIONSHIP.

Pros	• The dose consumed is known with certainty. • The number of people exposed and ill is known with certainty. • The health status of exposed individuals is known with more certainty.
Cons	• The data were obtained exclusively from healthy male volunteers, which prohibits any assessment of susceptible populations. • High doses of *Salmonella* were fed to volunteers, thus complicating extrapolation to low doses typically observed in outbreaks. • A limited number of serotypes were administered, and only one of these has been observed in the top five serotypes recorded by FoodNet. • The administered strains are different from those currently found in shell eggs and liquid egg products. • Data are lacking for the serotype Enteritidis that accounts for the majority of sporadic illnesses and outbreaks from shell eggs.

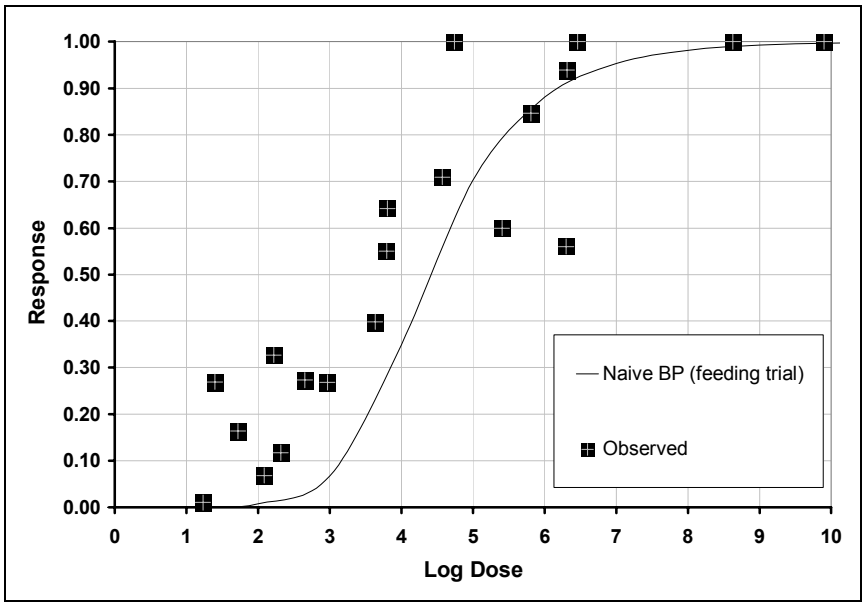

FIGURE 4-2 BETA-POISSON DOSE-RESPONSE MODEL FIT TO NAÏVE HUMAN FEEDING TRIAL DATA COMPARED WITH REPORTED OUTBREAK DATA. SOURCE: FAO/WHO.[2]

JEMRA outbreak dataset

JEMRA collected data from countries worldwide and identified 33 outbreaks that included quantitative information from which the dose and attack rate could be estimated (Table 4-2). Twenty-three of the 33 outbreak reports contained sufficient data on the number of people exposed, the number of people who became ill, and the number of organisms in the implicated food to be used in developing a dose-response relationship. Three of these outbreaks were

excluded because the immune status of the persons exposed could not be determined. In some outbreak reports, the data needed were incomplete and the number of people exposed, number of people ill, and/or the dose were/was estimated. The remaining 20 outbreaks comprise the database used to calculate a dose-response relationship.

Several *Salmonella* serotypes were associated with the outbreaks, including SE (12), *S.* Typhimurium (3), *S.* Heidelberg, *S.* Cubana, *S.* Infantis, *S.* Newport, and *S.* Oranienburg. Several vehicles were implicated, including food (meat, eggs, dairy products, and others), water, and a medical dye capsule (carmine dye). Eleven of the 20 outbreaks in the database occurred in Japan, and nine occurred in the U.S. Outbreak investigation reports provided by the Ministry of Health and Welfare of Japan provided a valuable source of information that expanded the database considerably (see text box).

The dataset assembled by Joint Expert Group is the most extensive set of real world information on dose and response for *Salmonella* spp. currently available, but it has limitations. JEMRA identified the most significant limitations of the dataset.

- Analysis of epidemiological reports indicates there are differences in responses (illness) between normal (between the ages of 5 and 65) and susceptible (less than 5 and greater that 65) human populations.[6] However, the outbreak dataset used by JEMRA does not contain detectable differences in response between normal and susceptible individuals. The inability of the JEMRA dose-response model to discriminate the response in these two populations may be due to the high level of uncertainty in the estimates for dose and number of people ill in the outbreak dataset. On the other hand, the association between salmonellosis and age may be due to reporting bias because children and the elderly with diarrhea may be more frequently cultured than other age groups.[7] In addition, confounding factors may be associated with behavioral characteristics of children (i.e., children eating snow, sand, or soil may be more likely to be exposed to *Salmonella* spp.).[8]

The Japanese Food Saving Program

The Japanese Ministry of Health and Welfare provided data from epidemiological investigations of foodborne illness outbreaks in Japan for use in the JEMRA risk assessment. This information was especially useful because it contained enumeration data on *Salmonella* spp. present in foods that made people ill. In Japan, large-scale cooking facilities which prepare more than 750 meals per day or more than 300 servings of a single menu item at a time, are advised (in accordance with a Japanese notification released in March 1997) to save food for future possible analysis in the event of an outbreak. This advice is also applicable to smaller-scale kitchens with social responsibility such as schools, day care centers, and other child-welfare and social-welfare facilities. Fifty-gram portions of each raw food ingredient and each cooked dish are saved for at least 2 weeks at temperatures lower than minus 20ºC. If an outbreak of foodborne illness occurs, public health personnel retrieve the samples, culture the saved food, and quantify the number of bacteria present.

- The endpoint measured in the outbreak dataset used by JEMRA was illness, but a standard definition for illness was not applied to all outbreaks. Illness is a process of cumulative damage to the host, leading to an adverse reaction. There are usually different and simultaneous symptoms of illness in any individual, and the severity of symptoms varies among hosts infected with the same pathogen. Illness is a process that is ideally

measured on a multidimensional, quantitative, and continuous scale (e.g., number of stools passed per day and body temperature).

- Analysis of data from human feeding trial studies did detect a difference in the response (infection) between some *Salmonella* serotypes. However, no difference was detected in the response (illness) between SE and other *Salmonella* serotypes in the outbreak dataset used by JEMRA. The significance of this discrepancy is uncertain given the difference in responses that were measured in the two datasets and the complex relationship between infectivity/virulence and serotype.

- The dataset used in the JEMRA dose-response model included outbreaks from both the U.S. and Japan. The U.S. population may differ from the Japanese population in susceptibility to *Salmonella* spp. Application of the JEMRA model to the U.S. population without considering differences in susceptibility at the population level could bias the results. The number of people exposed in Japanese outbreaks (~14,037, 52%) was about the same as that in U.S. outbreaks (~12,728, 48%) (Annex I, Table 3.14). The overall attack rate in the data was 21.8% (26,765 exposed, 5,636 ill). The attack rate among Japanese outbreaks (27.4%, range 16 to 100%) was higher than that of U.S. outbreaks (15.6%, range 1 to 100%). This was due in part to one large outbreak in the U.S. (8,788 people exposed) with an attack rate of 11.7% and one large outbreak in Japan (5,102 people exposed) with an attack rate of 26.9%. The overall attack rate was higher for Japanese outbreaks, but the median attack rate of U.S. outbreaks (55%) was higher than Japanese outbreaks (49%). Although differences in age and immune status between the two populations may exist, any potential effects appear to be small compared to the large amount of uncertainty in the dose-response relationship. Further, it is possible that the protocol of storing retained foods at 20°C may have reduced the number of salmonellae present and made survivors difficult to culture. These limitations of the JEMRA dose-response model were recognized, but we did not attempt to adjust the model for an exclusively U.S. population.

Dose-response models

JEMRA evaluated three existing dose-response models for *Salmonella* spp. using criteria developed by WHO for selecting mathematical models to interpret a dataset. The first model was the beta-Poisson model fit to the human feeding trial data for *Salmonella*.[9] The second model was proposed in the U.S. SE risk assessment[10] and was based on using a surrogate pathogen to describe the dose-response relationship. The third model, introduced in the Health Canada SE risk assessment, used a Weibull dose-response relationship updated to reflect outbreak information using Bayesian techniques. JEMRA concluded "…the dose-response model based upon the observed outbreak data provides an estimate for the probability of illness that is based on real world data. Given the assumptions associated with some of the other models the outbreak model offers the best current alternative for estimating the probability of illness upon ingestion of a dose of *Salmonella*." (Annex I, Figure I.19). JEMRA developed a beta-Poisson model (Equation 4.1) as the mathematical form for the relationship and this was fit to the outbreak data.

$$Pill = 1 - \left(1 + \frac{Dose}{\beta}\right)^{-\alpha} \quad (4.1)$$

The data from 34 outbreak studies provided JEMRA with the opportunity to develop a dose-response relationship. The beta-Poisson model was used for the dose-response relationship because it has been used successfully in previous risk assessments[9,10] and because it provided a good statistical fit to the data. A maximum likelihood estimation technique was used to estimate the parameters α and β from reported $\log_{10}$ dose and attack ratio response values obtained from the outbreak studies.

Point estimates of α and β were considered inadequate for use in the risk assessment because of the uncertainty in the outbreak data due to the uncontrolled conditions under which the data must be collected. Both the actual dose ingested and the true number of people exposed can be under- or overestimated. The uncertainty in the $\log_{10}$ dose and response data was described using a minimum and maximum value for each input for each of the 34 studies, as shown in Table 4-2.

Resampling techniques were used to generate synthetic data sets from each of the 34 ranges of $\log_{10}$ dose and response. The maximum likelihood technique was then used to estimate values of α and β for that resampled data set. This α and β pair was used to develop a single dose-response curve. This resampling process was repeated about 5,000 times. It generated 5,000 α and β pairs and 5,000 dose-response curves. Table 4-4 presents selected descriptive statistics for the 5,000 estimates of α and β.

TABLE 4-4 ALPHA AND BETA PARAMETERS USED IN DOSE-RESPONSE MODEL.

	Alpha	Beta
Expected value	0.1324	51.45
Lower bound	0.0763	38.49
2.5th percentile	0.0940	43.75
97.5th percentile	0.1817	56.39
Upper bound	0.2274	57.96

Source: FAO/WHO (2002).[2]

These parameters, in essence, enabled risk assessors to generate the range of dose-response curves shown in Figure 4-3. The squares indicate actual data points. The dark curve in the center represents the expected value of the dose-response relationship. The two adjacent curves represent the 2.5th and 97.5 percentiles, while the two outermost curves represent the lower and upper bounds on the dose-response relationship. Using the characterization of dose-response curves described here enabled risk assessors to address the uncertainty in the dose and response inputs quantitatively.

The draft reports of the Expert Group were reviewed by a group of internationally recognized experts twice during the course of work, and the final product was peer-reviewed and revised before completion. The thorough evaluation and review process is a strong point of the joint FAO/WHO dose-response model. However, all models are incomplete representations of the system they are intended to model.

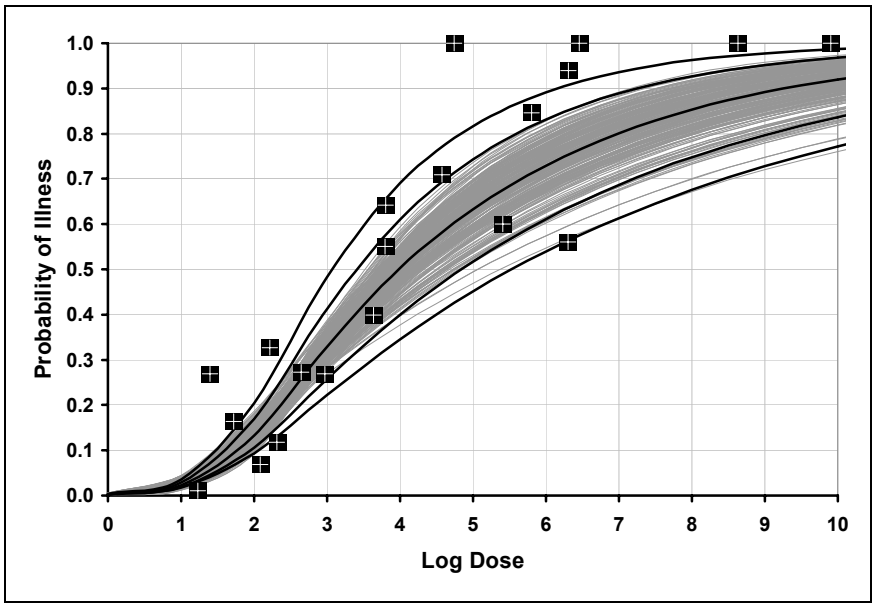

FIGURE 4-3 UNCERTAINTY BOUNDS FOR DOSE-RESPONSE CURVES, COMPARED WITH EXPECTED VALUE FOR THE OUTBREAK DATA. SOURCE: FAO/WHO.[2]

The dose-response model developed by JEMRA was selected for use in this risk assessment for the following reasons: the JEMRA model was developed through a process that incorporated the principles of transparency, peer review, and separation of risk assessment and risk management. The adherence to these principles provides some confidence in the results; the National Advisory Committee for Microbiological Contaminants in Foods (NACMCF) evaluated the model and determined it adequate for use in risk assessment; FDA is using the FAO/WHO model in their risk assessment of SE in shell eggs. Consistency with FDA will allow comparison of the results of the two assessments and meets Office of Management and Budget (OMB) guidelines.

The dose-response analysis presented here is combined with the exposure assessment described in the preceding chapter to develop the risk characterization in chapter 5.

ESTIMATES FROM SURVEILLANCE DATA

This section provides an estimate of yearly cases of illness, hospitalization, sequellae, and death from SE in eggs in the U.S., derived from public health surveillance systems. These independently derived estimates provide a benchmark to evaluate the plausibility of the probabilistic risk assessment. Dose-dependency of severity of salmonellosis is not considered in this risk assessment. However, there is evidence of a relationship between dose and severity of salmonellosis and other foodborne diseases.[11-14]

Passive surveillance of illness from non-typhoid *Salmonella* has been conducted for more than three decades in the U.S. Estimates of the yearly incidence rate from passive surveillance have been useful in tracking trends over time but they significantly underestimate the level of illness. Figure 4-4 shows the series of steps that must be met for an illness to be reported to the

CDC. Multipliers, ranging from 29[15] to 350,[16] have been developed to relate reported illness to total illnesses.

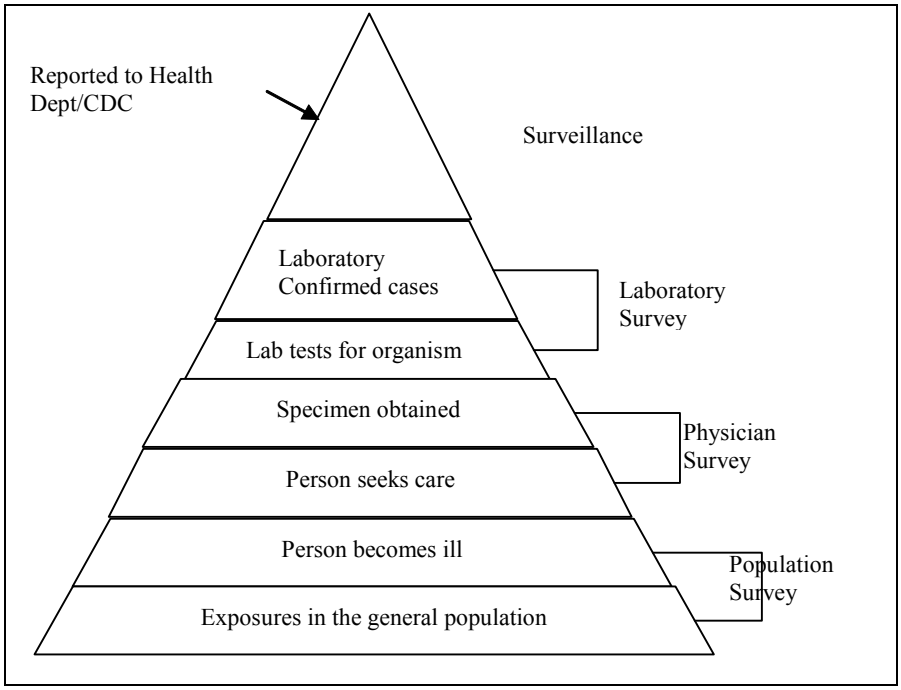

FIGURE 4-4 BURDEN OF ILLNESS PYRAMID.

In recent years the CDC instituted FoodNet to more accurately estimate the level of illness, hospitalization, and death from foodborne illness and to better define the performance of the surveillance system at all stages from infection to reporting of cases to CDC. However, cases of foodborne illness reported through the active surveillance system of FoodNet still represent only a fraction of the total number of illnesses. People who become ill may not seek medical care, physicians may not order bacterial stool cultures for patients with diarrhea, laboratories may not order the correct test, and illness reports may not be delivered.

Chalker and Blaser[17] developed a multiplier to estimate illness based on estimates of sequential artifacts within the national *Salmonella* surveillance system. Mead et al.[18] refined the estimates of sequential artifacts with results from surveys of laboratories, physicians, and the general population in the FoodNet system to estimate total illness from *Salmonella* and other foodborne pathogens in the U.S. Mead et al.[18] also calculated multipliers for underreported illnesses, *Salmonella*-specific hospitalization, and a *Salmonella*-specific case fatality rate (Table 4-5, Table 4-6, and Table 4-7). The underreporting multiplier developed by Chalker and Blaser[17] and the *Salmonella*-specific rates for hospitalization and death determined by Mead et al.[18] were used to estimate yearly illness, hospitalization, and death from SE in eggs in the U.S.

TABLE 4-5 SEQUENTIAL SURVEILLANCE ARTIFACTS IN THE STEPS FROM INFECTION TO ILLNESS REPORTING FOR *SALMONELLA*.[17]

Surveillance Step	Median Multiplying Factor	Factor Range Low	Factor Range High	No. of Studies	No. of Observations (all studies)
1. Infected person becomes ill	2.07	1.25	17.00	12	614
2. Patient consults a doctor	2.21	1.29	12.06	6	843
3. Doctor obtains culture	3.11	1.18	4.25	5	183
4. Laboratory identifies the organism	1.43	1.19	3.58	11	5,625
5. Laboratory reports to the health department	1.50	1.28	2.20	3	336
6. Health department reports to CDC	1.21	1.00	1.40	1	Unknown
Salmonella surveillance total multiplier	37		9,608		

Estimating Illness from *Salmonella* Enteritidis in Eggs

The calculations for estimating the yearly number of SE cases in the U.S. are described in this section and in Table 4-6. FoodNet data from the year 2000 reported 4,330 cases of illness from *Salmonella* spp. Of these 3,964 were serotyped. Of those serotyped, 585 isolates were identified as SE. The ratio of SE isolates to all serotyped isolates (585/3964) was multiplied by the number of *Salmonella* cases (4,330). The product, 639 SE cases, is an estimate of all cases (serotyped and unserotyped) caused by SE that occurred in the eight FoodNet catchment areas. Dividing the total number of cases (639) by the total population of the catchment area (30,500,000) provides the incidence of SE in the catchment area (2.1 cases/100,000 persons). The number of cases in the U.S. was estimated by multiplying the incidence rate in the catchment area by the U.S. population (281,400,000). The result, 5,896 reported cases, is an estimate of the number of reported SE cases from all causes in the U.S. in 2000 (Table 4-6).

Not all cases of illness from SE are reported. We repeated the work done by Chalker and Blaser[17] to calculate a multiplier relating reported illness to total illness from *Salmonella* spp. (Table 4-5). The multiplier of 37.0 was calculated by sequentially multiplying each of the surveillance step multipliers (1 through 6, Table 4-5). The value calculated in Table 4-5 (37) is slightly less than the value of 39 calculated by Chalker and Blaser. The reasons for the difference are shown in the appendix to this chapter. The multiplier from Table 4-5 was used to estimate the total number of illnesses from SE in the U.S. (217,946 infected) from the estimate of reported cases (5,896 reported cases).

TABLE 4-6 ESTIMATED ANNUAL ILLNESS FROM SE IN EGGS.

		Range		
Surveillance Step (see Table 4-5)	**Estimate**	**Low**	**High**	**Source of Estimate**
1. *Salmonella* illnesses reported to FoodNet	4,330			CDC[19]
2. Isolates serotyped	3,964			CDC[19]
3. Serotyped isolates that were Enteritidis	585			CDC[19]
4. Ratio of serotyped isolates that were Enteritidis	0.148			3 ÷ 2
5. Estimated number of illnesses from *Salmonella* attributable to Enteritidis	639			1 × 4
6. Population of the FoodNet catchment area	30,500,000			U.S. Census 2000
7. Incidence of SE in FoodNet catchment area	2.1/100,000			(5 ÷ 6) × 10^5
8. U.S. Population in 2000	281,400,000			U.S. Census 2000
9. Estimated cases of SE in U.S.	5,896			7 × 8
10. Illness underreporting multiplier	37.0	3.7	9,608	Table 4-5
11. Illness from SE	254,688	17,088	5.66 × 10^7	9× 10
12. Proportion of SE illness from eggs	0.8	0.68	0.95	Mishu et al.[20]; CDC[21,22]
13. Estimated annual SE illness from eggs	174,356	11,620	5.38 × 10^7	

Not all cases of illness from SE are the result of eating eggs. Mishu et al.[20] reported that 77% to 82% of vehicle-confirmed SE outbreaks were associated with grade A shell eggs. Between 1993 and 1997, on average, 80% of vehicle-confirmed outbreaks were egg-associated, with a range of 68% to 95%. In 1998, of the 18 outbreaks for which a vehicle could be confirmed, 15 (83%) were associated with eggs.[21] In 1999, of the 19 outbreaks for which a vehicle could be confirmed, 15 (79%) were associated with eggs.[22] The proportion of SE cases that are due to consuming eggs was estimated to be 80%. The range of this proportion extends from 0.68 to 0.95. The result is an estimate of about 174,356 (range 12,000 to 54 million) yearly cases of illness from SE in eggs.

Estimating Hospitalizations from *Salmonella* Enteritidis in Eggs

A fraction of the persons who become ill from SE in eggs are hospitalized. Mead et al.[18] calculated a *Salmonella*-specific hospitalization rate from FoodNet data of 0.221. More recent information from FoodNet suggests that hospitalization rates varied for the four major serotypes (*S.* Typhimurium, SE, *S.* Heidelberg, and *S.* Newport) isolated from human illness cases from 0.1 for *S.* Newport to 0.22 for *S.* Heidelberg.[23] The rate of hospitalization for SE was 0.15 (322 hospitalization ÷ 2,144 cases). The annual number of hospitalizations from SE in eggs was estimated using the methodology developed by Mead et al.[18] and the SE-specific hospitalization rate provided by Finke et al.[23] (Table 4-7). The range of hospitalization rates from the most frequently isolated *Salmonella* serotypes of 0.1 to 0.22 respectively was used as lower and upper bounds for this estimate.[23]

Not all hospitalizations are reported because the condition leading to hospitalization may be a sequella that developed well after resolution of the actual infection. Mead et al.[18] used a multiplier of two to derive an estimate of the total number of hospitalizations from reported hospitalizations, correcting for underreporting. The lower bound for the estimate is 1 because it seems plausible that all hospitalizations are reported. The upper bound was arbitrarily set at 3. The estimate for hospitalizations from all SE was calculated by multiplying the reported hospitalizations by the underreporting multiplier. The product is an estimate of all hospitalizations (reported and unreported) caused by SE. Not all hospitalization caused by SE are the result of eating eggs. The estimate for hospitalization (reported and unreported) was multiplied by the proportion of SE illnesses that resulted from consuming eggs (0.8). The product is our estimate of the total yearly hospitalizations in the U.S. resulting from SE in eggs. The estimate from Table 4-7 shows between 601 and 2,519 with a most likely estimate of 1,440 hospitalizations annually due to SE in eggs.

TABLE 4-7 ESTIMATED ANNUAL HOSPITALIZATIONS FROM SE IN EGGS.

		Range		
	Estimate	**Low**	**High**	**Source of Estimate**
1. Estimated cases of SE in the United States	5,896			Table 4-5
2. SE-specific hospitalization rate	0.15	0.1	0.22	Finke et al.[23]
3. Hospitalizations (reported)	884	590	1,297	1 × 2
4. Hospitalization underreporting factor	2	1	3	Mead et al.[18]
5. Hospitalizations (reported and unreported	1,768	884	2,652	3 × 4
6. Proportion due to eggs	0.8	0.68	0.95	Mishu et al.[20]
Total hospitalizations from SE in eggs	1,440	601	2,519	4 × 5

Estimating Deaths from *Salmonella* Enteritidis in Eggs

A fraction of persons who become ill from SE in eggs die. Mead et al.[18] estimated a *Salmonella*-specific death rate from reported cases of 0.0078. The annual number of deaths from SE in eggs was estimated using Mead et al.'s[18] methodology (Table 4-8). The reported cases of illness from *Salmonella* spp. were multiplied by the *Salmonella*-specific death rate. Deaths, like hospitalizations, are underreported because pathogen-specific surveillance systems rarely collect information on illness outcome, and outcome-specific surveillance systems (e.g., death certificates) grossly underreport many pathogen-specific conditions.[18] The multiplier used by Mead et al.[18] for underreported deaths is two. The lower bound for the estimate is one because it seems plausible that all deaths are reported. The value of 3.1 was used as an upper bound. Consequently, deaths from egg-related SE infections are estimated to be between 75 and 139, with a most likely value of 75 annually.

TABLE 4-8 ESTIMATED ANNUAL DEATHS FROM SE IN EGGS.

		Range		
	Estimate	**Low**	**High**	**Source of Estimate**
1. Estimated cases of SE in the U.S.	5,896			Table 4-5
2. SE-specific death rate	0.0078			Mead et al.[18]
3. Reported deaths	47			1 × 2
4. Death underreporting factor	2	1	3.1	Mead et al.[18]
5. Estimated deaths	94	47	146	3 × 4
6. Proportion due to eggs	0.8	0.68	0.95	Mishu et al.[20] CDC[19,24]
7. Total deaths from eggs	75	32	139	

Estimating Sequellae from *Salmonella* Enteritidis in Eggs

The sequellae reported in a review of 55 journal publications on *Salmonella* infection included reactive arthritis, urethritis, conjunctivitis, entesopathy, myalgia, weight loss of over 5 kg., dactylitis, erythema nodosum, oral ulcers, myocarditis, acute anterior uveitis, iritis, cholecystitis, keratitis, pharyngitis, and pneumonia.[25] In an outbreak among 473 police officers, 340 responded to a questionnaire and 196 (57%) individuals reported extra-enteric symptoms.[26] In another study of 210 cases, 191 responded and 143 (75%) of those reported extra-enteric symptoms.[27] The results of these two studies are summarized in Table 4-9.

The most severe sequellae of *Salmonella* infection is probably reactive arthritis. Symptoms commonly develop 7 to 30 days after intestinal illness. The knee is often affected along with other peripheral joints. Reiter's syndrome, considered a special case of reactive arthritis, typically includes three symptoms: asymmetric arthritis in knees and ankles, non-specific urethritis, and conjunctivitis.[28] Roughly 2 to 3 % of people who become ill from *Salmonella* spp. develop reactive arthritis.

TABLE 4-9 RANKING OF SEQUELLAE FROM *SALMONELLA* INFECTION.

***Salmonella* Typhimurium PT 22[26]**		***Salmonella* Bovismorbificans[27]**	
Headaches	182 (53.5%)	Articular symptoms	66 (35%)
Joint pain	106 (31.2%)	Headaches	52 (27%)
Redness or soreness in the eyes	37 (10.9%)	Eye symptoms	8 (4%)
Soreness in the mouth	15 (4.4%)	Cutaneous symptoms (one erythema nodosum)	7 (4%)
Skin rash	10 (2.9%)		
Total extra-enteric symptoms	196	Total extra-enteric symptoms	143

This chapter estimates yearly cases of illness, hospitalization, and death from egg-associated SE in the U.S. as shown in Table 4-10. The median hospital stay for patients in one study was 4 days.[23] Two to three percent of ill persons, about 4,000 to 6,000 persons, could later develop reactive arthritis and 0.5 to 1.0% of ill persons, about 1,000 to 2,000 persons, could develop another sequella of infection.

TABLE 4-10 ESTIMATED YEARLY CASES OF ILLNESS, HOSPITALIZATION, SEQUELLA, AND DEATH FROM SE IN EGGS.

Outcome	Estimate (per annum)
Illness	174,356
Hospitalization	1,440
Chronic sequella	6,622
Death	75

SUMMARY

This chapter considered the data available to model a dose-response relationship for *Salmonella* spp. and the beta-Poisson model produced by the Joint Expert Meetings on Microbiological Risk Assessment (JEMRA). The strengths and weaknesses of the JEMRA model were discussed as well as reasons for selecting the JEMRA model for use in this risk assessment. This dose-response relationship is used in this risk assessment to estimate illness from exposure. These independently derived estimates provide a benchmark for comparing the results of a probabilistic model and will allow testing plausibility of the modeling results.

APPENDIX

Synopsis and review of the rationale for the multipliers developed by Chalker and Blaser.[17]

Surveillance Step 1—Persons who are infected become ill (i.e., show clinical signs of illness)

Proportion	*Multiplier*	*Number Sampled*	*Reference*	*Comments*
0.5	2.0	225	Onogawa et al.[29]	In a "large" study of children and food handlers in Tokyo, 50% of culture-proven handlers had symptoms. A total of 1,258,801 fecal samples, obtained from 816,965 pupils and 441,836 food handlers, were examined for the presence of *Salmonellae*. Of those samples collected from pupils, 1022 (0.13%) were positive for *Salmonellae*; of those samples collected from food handlers, 314 (0.07%) were positive for *Salmonellae*. In the conclusions appendix to this article, it is stated that about 50% of *Salmonella* carriers had such complaints as mild diarrhea, stomachache, and nausea. Unfortunately, it is not clear if this ~50% value was derived from information on all asymptomatic carriers, or, as presented in Figure 3 of the manuscript, this value was derived from the retrospective survey of 2,215 healthy carriers. The body of the text of the article is in Japanese; therefore, we were unable to determine if this point is clarified in the article per se.
0.55	1.8	9	Blaser et al.[30]	In a restaurant outbreak of salmonellosis, 5 (55%) of 9 culture-positive employees had symptoms.
0.69	1.4	59	Palmer et al.[31]	A retrospective survey of those involved in a college residence hall outbreak showed that 41 (69%) of 59 culture-positive students had symptoms.
0.07	2.1	15	CDC (see Chalker and Blaser[17])	One (7%) of 15 culture-positive nursing home employees had symptoms following a salmonellosis outbreak (unpublished CDC communication, no date given).
0.08	13.0	13	CDC (see Chalker and Blaser[17])	In a hospital outbreak, 1 (8%) of 13 culture-positive personnel surveyed had symptoms (unpublished CDC communication).
0.06	17.0	17	CDC (see Chalker and Blaser[17])	In a New York City hospital outbreak, 1 (6%) of 16 culture-positive dietary personnel had symptoms (unpublished CDC communication, no date given (Chalker and Blaser point out data involving food-handling employees may be skewed by reluctance to admit having had symptoms).
0.27	3.7	11	Rice et al.[32]	In a nosocomial outbreak in Puerto Rico, 3 (27%) of 11 culture-positive patients had symptoms.
0.8	1.3	55	Koplan et al.[33]	Forty-four (80%) of 55 persons were symptomatic following a summer camp outbreak in Trinidad.
0.23	4.3	69	Wilkie et al.[34]	In an English nursing home outbreak, 16 (23%) of 69 culture-positive individuals had symptoms.
0.43	2.3	7	Ryder et al.[35]	In a nosocomial outbreak linked to contaminated milk, 3 (43%) of 7 culture-positive infants had symptom.
0.34	1.9	64	Payne and Scudamore[36]	Thirty-four (54%) of 64 culture-positive individuals had symptoms following an outbreak in England.
0.66	1.6	70	Gill et al.[37]	In an outbreak linked to chocolate bars, 43 (66%) of 70 culture-positive household contacts surveyed reported symptoms.

2 – Persons who are ill consult a doctor				
Proportion	*Multiplier*	*Number Sampled*	*Reference*	*Comments*
0.08	12.1	386	CDC[38]	During a *Salmonella* outbreak on a Caribbean cruise ship, 32 (8%) of 386 passengers who became ill sought the ship's doctor.
0.77	1.3	22	CDC[39]	In an outbreak linked to ice cream, 17 (77%) of 22 ill patients sought a doctor (Chalker and Blaser point out here the dose of *Salmonella* ingested may have been high).
0.58	1.7	22	Bollegraaf[40]	In a common-source outbreak affecting Canadian executives, 26 (58%) of 45 ill individuals consulted a doctor.
0.37	2.7	232	CDC (see Chalker and Blaser[17])	As determined by a retrospective questionnaire, 86 (37%) of 232 college students who became ill following a *Salmonella* outbreak sought medical aid.
0.36	2.8	91	CDC (see Chalker and Blaser[17])	Following a *Salmonella* outbreak on a Navajo Indian reservation, 33 (36%) of 91 ill individuals received prescriptions for paregoric (unpublished CDC report). Chalker and Blaser assumed all symptomatic persons seen as outpatients received this prescription Data are not provided with which to judge the strength of the authors' assumption.
0.72	1.4	67	Rice et al.[32]	Following an outbreak of salmonellosis at a summer camp, 48 (72%) of 67 acutely ill patients visited a doctor.

3- Doctor obtains culture				
Proportion	*Multiplier*	*Number Sampled*	*Reference*	*Comments*
0.66	1.5	32	CDC[38]	Of 32 people who reported being acutely ill to a cruise ship's doctor, specimens were obtained from 21 (66%).
0.86	1.2	80	McCall et al.[41]	At a Tennessee hospital for the mentally retarded, specimens obtained from 68 (86%) of 80 patients with acute gastroenteritis were cultured.
0.32	3.1	28	Rosenberg et al.[42]	About 40% of *Shigella*-associated diarrhea presents with gross blood in the stool, an observation that might be expected to cause an increase in the proportion of samples sent for culture
0.24	4.3	17	CDC[39]	In an ice cream-related outbreak of salmonellosis in Georgia, 4 (24%) of 17 ill persons who visited a physician had specimens taken for culture.
0.42	2.4	26	Bollegraaf[40]	Eleven (42%) of 26 ill Canadian executives who visited a doctor had specimens taken.

4 -Laboratory identifies the organism

Proportion	*Multiplier*	*Number Sampled*	*Reference*	*Comments*
0.84	1.19	4,374	Gavan[43]	In a 1972 quality evaluation, the College of American Pathologists found that 84% of 4,374 laboratories that were one of 20 common bacterial pathogens were able to identify it correctly.
0.83	1.20	800	CDC[44]	In 1975, the CDC evaluated ca. 800 laboratories in the U.S. and found that 83% were able to correctly isolate and identify *Salmonella*.
0.34	1.29	79	Bengtsson et al.[45]	During an outbreak of *Salmonella* Typhimurium in Sweden, 27 (34%) of 79 people with negative stool cultures had a subsequent seroconversion to *Salmonella.*
0.77	2.93	66	Palmer et al.[31]	*Salmonella* was isolated from stools of 77% of college students from an affected residence hall who presented with acute gastroenteritis during a common-source outbreak.
0.42	2.35	54	CDC (see Chalker and Blaser[17])	Twenty-three (42%) of 54 culture specimens from ill patients were positive for *Salmonella* Enteritidis following an outbreak of salmonellosis in a nursing home.
0.71	1.43	63	Koplan et al.[33]	Forty-four (71%) of 63 acutely ill patients at a summer camp in Trinidad developed positive cultures.
0.57	1.76	44	Lowenstein[46]	Stools from 25 (57%) of 44 ill persons were positive.
0.40	2.50	85	Armstrong et al.[47]	Following a point-source outbreak, 34 (40%) of 85 stool specimens from acutely ill persons yielded positive cultures.
0.83	1.20	6	CDC[39]	During a series of multiple *Salmonella* outbreaks in the northeast U.S. and linked to precooked roast beef, five (83%) of 6 stool specimens from symptomatic subjects were positive.
0.28	3.58	43	Spitalny et al.[48]	During *Salmonella* outbreaks in Vermont, 12 (28%) of 43 cultured specimens from acutely ill subjects were positive.
0.82	1.22	11	Bollegraff[40]	In an outbreak among Canadian men, nine (82%) of 11 cultures obtained were positive.

5 -Laboratory reports to the health department				
Proportion	*Multiplier*	*Number Sampled*	*Reference*	*Comments*
0.67	1.50	42	Vogt et al.[49]	The value of 56% given by Chalker and Blaser only takes into account data from 1983 in which 24 of 42 cases were reported to the health department. Data from 1982 indicate 18 of 21 (86%) of salmonellosis cases were reported. If data from 1982 and 1983 are combined, we find that 42 of 63 (67%) of cases were reported; thus, the multiplier is adjusted to 1.5, and the median of the three studies is 1.5.
0.42	2.20	11	Marier[50]	The number of samples here (11) is actually the number of hospitals surveyed and not the number of positive bacterial isolates identified by a laboratory.
0.78	1.28	262	Godes et al.[51]	Of 262 clinical laboratories in Minnesota, 78% of *Salmonella* infections were reported to the state health department.
	2.20	?	Thacker et al.[52]	Upon institution of an active surveillance system in Rochester, New York, a 2.2-fold increase was found in the number of cases reported compared to earlier surveillance systems.

6. Health department reports to CDC				
Proportion	*multiplier*	*Number sampled*	*Reference*	*Comments*
0.83	1.2	100*	Thacker et al.[52]	Because only one study was reported, we assumed a range extending from 1.0 to 1.4.

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