Public Health Outcomes Module

A. Summary of the Public Health Outcomes Module

The Public Health Outcomes Module links the exposure to SE in shell eggs and egg products with the adverse health outcomes of morbidity and mortality which may arise from the ingestion of SE bacteria (Fig. E-1). These health outcomes include infection without illness, infection with illness, and the consequences of illness which may include physician visits, medical treatment, hospitalization, post-infection sequelae, and death. The outcome from a single exposure to SE from shell eggs or egg products for the individual varies widely and is a function of the individual's age, health status, immune status, the number of SE bacteria consumed, the fat content of the food vehicle, and other factors such as pregnancy and underlying liver disease or kidney disease. The outcomes of the Public Health Outcomes Module are the primary measure of the public health consequences of exposure to SE from shell eggs and egg products. This module may be used as the primary indicator of the public health benefits of specific risk mitigations introduced into other modules within the SE Risk Assessment Model.

The subsequent sections discuss the following elements of the module:

module structure

distributions used to specify module parameters

module outputs for a specific number of persons exposed to a specific dose

sensitivity analysis to determine the parameters which most influence the module outputs and limitations of the Public Health Outcomes Module.

Public Health Outcomes Module

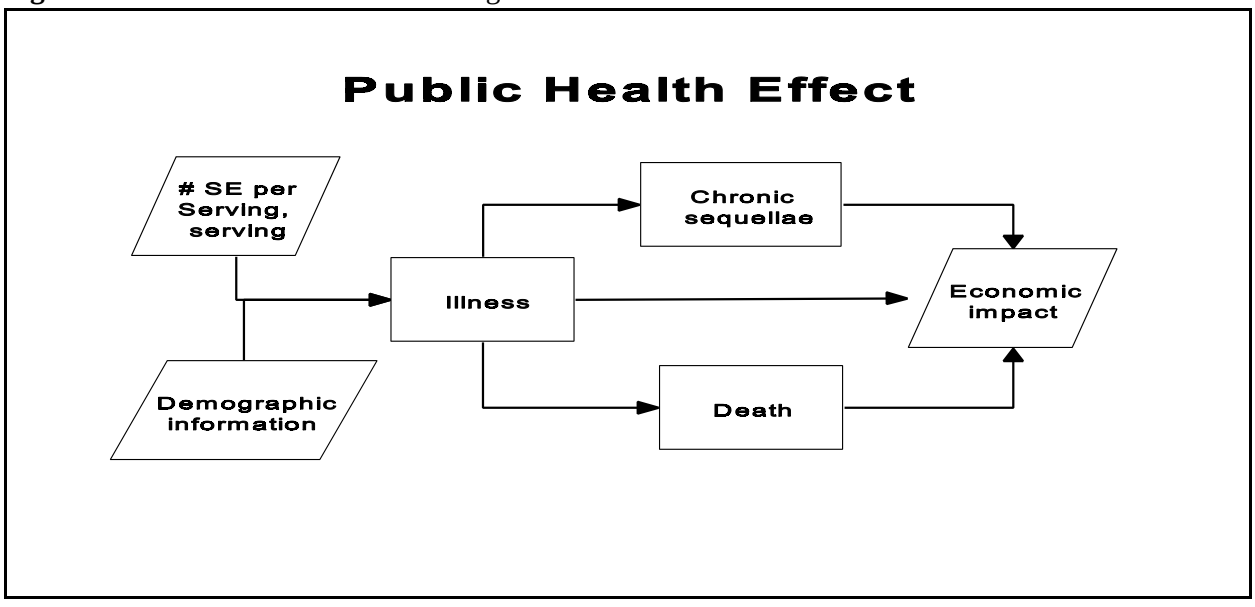
1. **Overall Structure of the Public Health Outcomes Module and the Relationship of the Public Health Outcomes Module to SE Risk Assessment Model**

   In the context of the entire SE risk assessment model, the Public Health Outcomes Module receives inputs from the Preparation and Consumption Module. Thus the Public Health Outcomes Module indirectly incorporates inputs from all other preceding modules (see figure above and Fig. E-1). The public health impacts of exposure to SE through shell eggs and egg products are computed in terms of numbers of illnesses and specific case outcomes on an annual basis. The relative worth of specific risk mitigation efforts to reduce exposure to SE in shell eggs and egg products is measured in terms of the outputs of the Public Health Outcomes Module. Although morbidity and mortality have measurable economic impacts, the economic costs of illness and the economic costs and benefits of mitigation activities are not included in this module.

2. **Basic Module Flow**

   This section contains a brief, non-mathematical description of the Public Health Outcomes Module, and the specific inputs to the module, and the specific outputs produced by the module. A more detailed and mathematical presentation of the module, and the distributions of the input and output variables, and the specific details of the modeling algorithms are found in the sections which follow.

Figure E-1 Flow of Data Into and Through the Public Health Outcomes Module



Public Health Outcomes Module

A more detailed diagram of the structure of the Public Health Outcomes Module is shown in Fig. E-2. Fig. E-2 illustrates the basic form of the Public Health Outcomes Module and its outputs. The flow of data in the module and the information generated by the Public Health Outcomes Module are as follows:

a. A given number of people are each exposed to a specific dose of SE bacteria.

b. The population of people exposed to SE is partitioned into two sub-populations. One sub-population is assumed to be in good health and is referred to as a 'normal sub-population' in order to reflect the level of risk for disease from SE in shell eggs and egg products which is usually seen in the general population. The second sub-population is referred to as the 'susceptible sub-population'. The susceptible sub-population is composed of persons who are at increased risk of illness from SE in shell eggs and egg products. This susceptible sub-population includes the elderly, newborn infants, persons with immunodeficiency from treatment for cancer, pregnant women, persons with chronic illness (e.g. diabetes or rheumatoid arthritis), and persons with HIV infections and AIDS. For the purposes of this module, the assumption is made that both sub-populations have the same food consumption patterns. However, it is recognized that some sub-populations (not defined here) may consume foods which utilize raw or undercooked eggs.

c. For each sub-population, the probability of an individual person within a sub-population becoming ill from exposure to a specified dose of SE from shell eggs and egg products is calculated using a stochastic dose-response function that incorporates the uncertainty in parameters of the dose-response function.

d. From the number of persons exposed and the computed probability of becoming ill from exposure to a specified dose of SE from shell eggs and egg products, the distribution of the number of persons becoming ill in each sub-population (normal and susceptible) is computed. It should be noted that not every person exposed to the dose of SE becomes ill. The ill persons in each sub-population are then partitioned into four mutually exclusive groups based on clinical outcomes after exposure to the SE and the development of illness. The mutually exclusive clinical outcomes are:

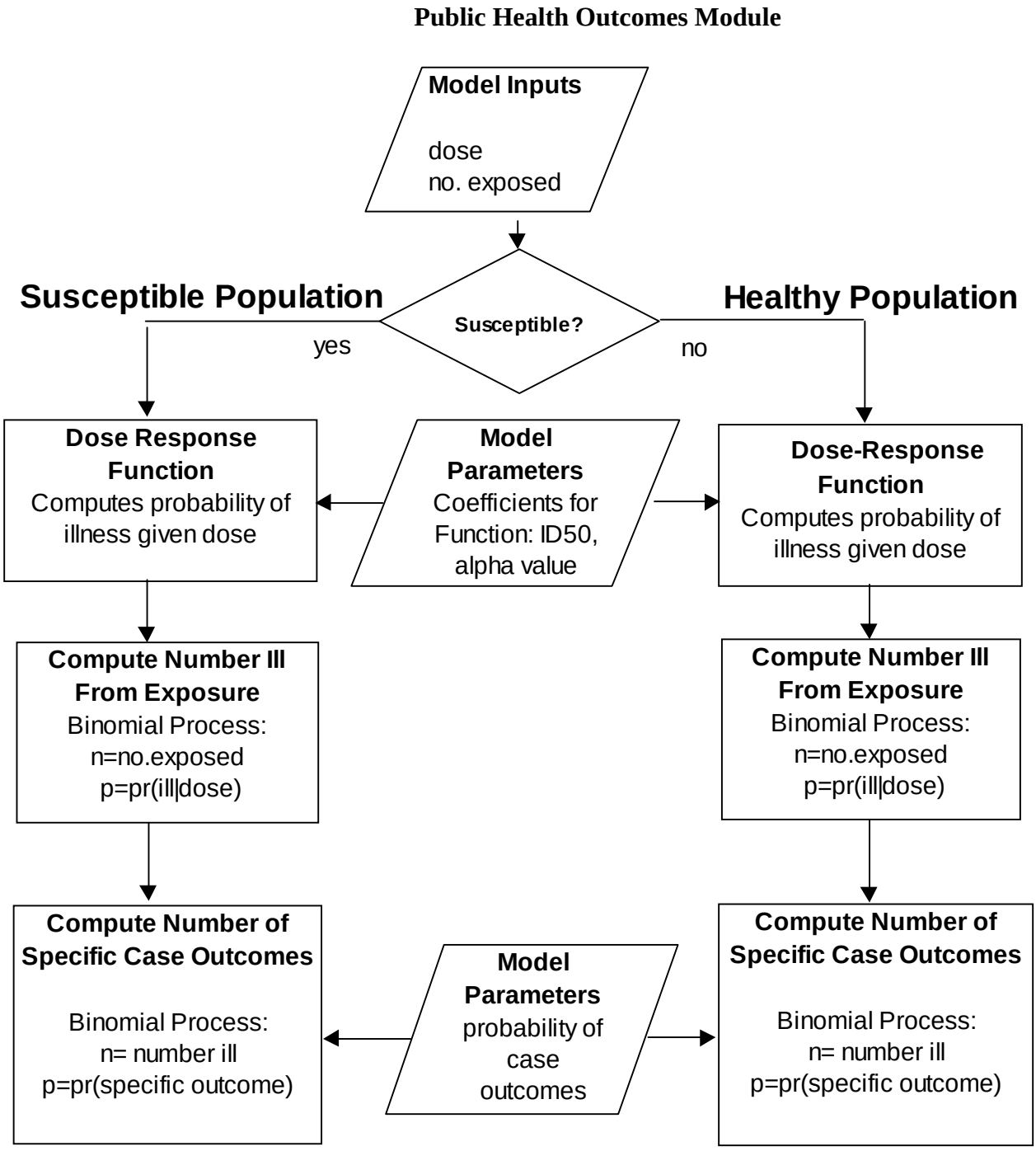
   (1) Recovery from illness with no medical treatment

   (2) Treatment by a physician with recovery from illness

   (3) Hospitalization and subsequent recovery from illness

   (4) Death from infection with SE from shell eggs and egg products

   (5) Development of long-term sequelae such as reactive arthritis after the SE infection.



B. Inputs, Parameters, and Variables for the Public Health Outcomes Module

1. Definitions: Each of the parameters used in the Public Health Outcomes Module has a distribution of possible outcomes. The Public Health Outcomes Module contains four distinct types of data: inputs, explicit parameters, implicit parameters, and state variables. Each of these four distinct types of data are defined below.

a. Inputs: Input values to the Public Health Outcomes Module are variables created in the Preparation and Consumption Module. These inputs are exogenous to the Public Health Outcomes Module and are not subject to modification within the Public Health Outcomes Module.

b. Explicit parameters: Explicit parameters are explicitly described as scalars or random variables within the Public Health Outcomes Module. Changes in the inputs to the Public Health Outcomes Module or to the structure of the Public Health Outcomes Module do not change the value of an explicit parameter. An example of an explicit parameter is the probability of visiting a physician given a person is ill.

c. Implicit parameters: Implicit parameters are derived solely from the explicit parameters and are not influenced by the inputs to the Public Health Outcomes Module or the structure of the Public Health Outcomes Module. Implicit parameters function in the same way as explicit parameters and are derived by an algebraic combination of explicit parameters instead of being explicitly specified as scalars or distributions. In the Public Health Outcomes Module, the implicit parameters are used to specify rate variables which describe the probability or rate of persons in one state of health moving into another state of health. An example of an implicit parameter is the probability of not visiting a physician given that a person is ill.

d. Output Variables and State Variables: The term ‘state variable’ refers to variables which describe the various states of health in which an ill person can be found, including temporary states such as “ill”. The output variables, which the Public Health Outcomes Module tracks, are state variables which describe permanent states of health, e.g., recover without medical treatment. Output variables and state variables are derived by an algebraic combination of inputs to the module, explicit parameters, and implicit parameters.

The specific module inputs, explicit parameters, implicit parameters, and output variables are described in the following section.

2. Input Variables From The Preparation & Consumption Module

a. Dose: The Preparation and Consumption Module (which takes inputs from other preceding modules in the SE Risk Assessment Model) provides the input variable of dose in the form of the number of viable and infectious SE bacteria that are present after food preparation activities. The entire dose of SE bacteria is assumed to be ingested by every member of the exposed population.

b. Number of persons exposed: The Preparation and Consumption Module provides the number of persons who are each exposed to the specified dose.

c. A total of 60 pairs of ‘dose-number exposed’ are given as input to the Public

Health Outcomes Module from the Preparation and Consumption Module in order to fully represent the full range of doses to which the population is exposed. For example, the Preparation and Consumption Module may say that the range of the dose to which the population is exposed is between 10 SE bacteria and 1000 SE bacteria. Not everyone will receive 10 SE bacteria and not everyone will receive 1000 SE bacteria. There will be a certain number of persons in the exposed population who will receive a specific dose. It is this pairing of 'dose' and 'number exposed' which is given as input to the Public Health Outcomes Module, and there are 60 of these 'dose-number exposed' pairs which are given to the Public Health Outcomes Module in order to determine the number ill persons and the types of illnesses based on the input from the Preparation and Consumption Module.

3. Explicit Parameters

Although the Public Health Outcomes Module includes many implicit parameters and other variables, there are only ten explicit parameters. These ten explicit parameters and the inputs from the Preparation and Consumption Module drive the Public Health Outcomes Module. The evidence and specifications of the ten explicit parameters are covered in the section titled "D. Parameters in the Public Health Outcomes Module: Evidence and Specification". Table E-1 contains a summary of the explicit parameters and the implicit parameters and the derivation of the implicit parameters. The ten explicit parameters are described below.

a. The first explicit parameter is the probability of a person being in a sub-population which is more susceptible to illness from exposure to SE from shell eggs and egg products.

b. The probability of becoming ill after ingesting a specific dose of SE bacteria is also an explicit parameter which is calculated for each sub-population so that two explicit parameters are produced. These two explicit parameters are calculated from a dose-response function which is further described in the section titled: "E. Probability of Infection: Microbial Dose-Response Modeling".

c. Six conditional probabilities describing three clinical outcomes of illness for each of the two sub-populations (specified separately for the normal sub-population and for the susceptible sub-populations, thus totaling six parameters). These conditional probabilities are

(1) The probability of seeing a physician given the person is ill, denoted by the expression: Pr(physician visit | ill);

(2) The probability a person is hospitalized given they are being treated by a physician, denoted by the expression:
Pr(hospitalized | treated by physician).

(3) The probability a hospitalized person dies, denoted by the expression: Pr(death | hospitalized).

d. The last explicit parameter is the probability of developing a sequela of an infection with SE after recovering from the initial illness due to SE from shell eggs and egg products. In this module, the probability of developing reactive arthritis is the only post-illness sequela which is modeled.

4. Implicit Parameters

Several parameters of the Public Health Outcomes Module are not specified directly, (i.e. explicitly) but are derived from the explicit parameters. These implicit parameters are (see also Table E-1):

a. Probability that a person exposed to SE from shell eggs and egg products is in the normal sub-population with respect to susceptibility to pathogens.

b. Probability of final clinical outcomes of illness which are conditioned on a person being ill after ingesting a specific dose of SE bacteria. This probability is derived separately for susceptible sub-populations and for normal sub-populations.

c. Probabilities of recovery from the various clinical outcomes of gastroenteritis due to SE are not entered as parameters; they are derived from three implicit parameters, which are the three conditional probabilities listed:

Pr(physician visit | ill)

Pr(hospitalized | treated by physician)

Pr(death | hospitalized).

Table E-1. Explicit and Implicit Parameters in Public Health Outcomes Module [1,2]

Explicit Parameter	Implicit Parameter	Derivation of Implicit Parameter
Pr(susceptible)	Pr(normal)	1 - Pr(susceptible)
Pr(physician visit|ill)	Pr(recover without medical treatment)	1 - Pr(physician visit|ill)
Pr(hospitalized|physician visit)	Pr(recover without being hospitalized|physician visit) [3]	1 - Pr(hospitalized|physician visit)
Pr(death|hospitalized)	Pr(recover|hospitalized)	1 - Pr(death|hospitalized)
Pr(reactive arthritis|ill)		
ID_n :Public Health Outcomes parameter for normal sub-population	ID_s :dose parameter for susceptible sub-population	$ID_n \div 10$
	Pr(see physician and recover without hospitalization)	Pr(physician visit|ill) × {1-Pr(hospitalize |physician visit)}
	Pr(see physician, are hospitalized, recover)	Pr(physician visit|ill) × Pr(hospitalized|physician visit) × {1 - Pr(death|hospitalized)}
	Pr(death)	Pr(visit physician|ill × Pr(hospitalized|physician visit) × Pr(death|hospitalized)

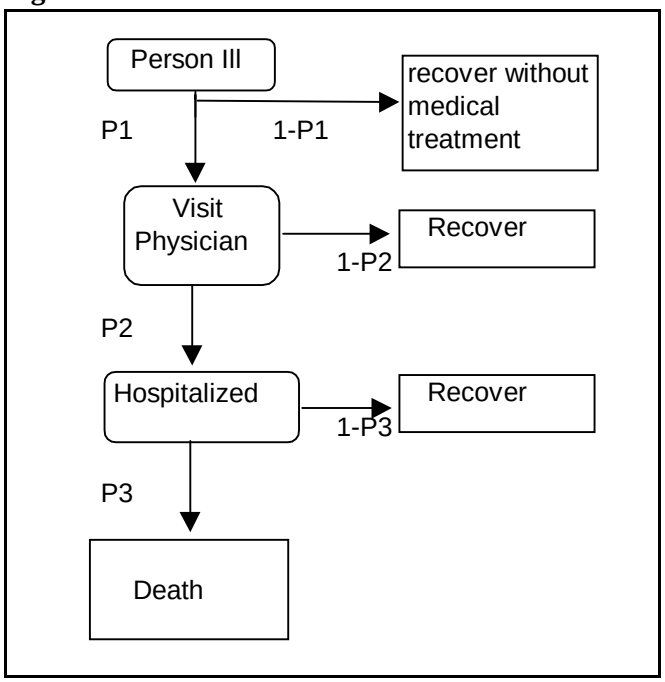
[1] All parameters are specified separately for susceptible and normal sub-populations except for pr(reactive arthritis).

[2] Derivation of implicit probabilities of clinical outcomes is contained in Module Parameters section of text. All conditional and unconditional probabilities of clinical outcomes are for ill persons.

[3] Persons who are treated by a physician and recover without being hospitalized.

Fig. E-3 shows the relationship between the explicit parameters associated with illness, visiting a physician, and the implicit parameters associated with recovery without treatment, recovery after physician visit, recovery after being hospitalized.

Figure E-3. Outcomes of Illness



With the conditional probabilities:[1]

P1 = Pr(physician visit | ill)

P2 = Pr(hospitalized | physician visit)

P3 = Pr(death|hospitalized) and their compliments

1-P1 = Pr(recover without medical treatment)

1-P2 = Pr(recover without being hospitalized | treated by physician)

1-P3 = Pr(recover | hospitalized).

The implicit parameters are derived from and are consistent with the probability axioms:

(1) for a Bernoulli random variable without outcomes A and Å, where Å equals "not A", Pr(Å) = 1 - Pr(A)

(2) for events A and B, probability of both A and B occurring = $Pr(A \cap B) = Pr(A)Pr(B|A)$

(3) for independent events A, B, and C, probability of A, B, and C occurring = $Pr(A \cap B \cap C) = Pr(A)Pr(B)Pr(c)$.

The probabilities of the final outcomes are computed as follows:

(1) Pr(recover without medical treatment) = 1-P1

[1] Notation: Pr(A) is read as "the probability of A occurring"; Pr(A|B) is read as "the probability of A occurring given B occurs or has occurred".

(2) Pr(physician visit and recover) =
Pr(physician visit|ill) * Pr(recover without being hospitalized|physician visit) =
P1 * (1-P2)

(3) Pr(hospitalized and recover) =
Pr(physician visit|ill)*Pr(hospitalized|physician visit)*Pr(recover|hospitalized) =
P1 * P2 * (1-P3)

(4) Pr(death) =
Pr(physician visit|ill) * Pr(hospitalized|physician visit) * Pr(death|hospitalized) =
P1 * P2 * P3

The specific case outcomes are mutually exclusive. For example, those persons who were hospitalized are assumed to have seen a physician prior to being hospitalized and are included in the group who saw a physician and were hospitalized; they are not included in the group who saw a physician and were not hospitalized. The values of the implicit parameters and the explicit parameters are estimated separately for the susceptible sub-population and for the normal sub-population.

5. Module Outputs

In the Public Health Outcomes Module the following outputs are estimated for both the susceptible sub-population and the normal sub-population and are separately presented as totals for the susceptible sub-population and for the normal sub-population as well as for the entire U.S. population. These outputs are for all cases and outcomes for the time period of one year.

a. Number exposed

b. Number ill

c. Number with specific clinical outcomes:

(1) Recover with no treatment

(2) Are treated by a physician and recover without being hospitalized;

(3) Are hospitalized and recover;

(4) Are hospitalized and die;

(5) Develop reactive arthritis after recovering from SE infection.

d. Indicators of case-fatality rates:

(1) Proportion of those ill who die (number deaths/number ill)

(2) Deaths per 100,000 persons ill.

The outputs of the Public Health Outcomes Module include the uncertainty contained in all related variables in both the Public Health Outcomes Module as well as all previous modules. The outcomes are expressed as probability distributions rather than constants. In addition to specific summary statistics for each outcome variable (mean, minimum, maximum, and 90% confidence limits), a frequency distribution for each output is presented in graphic form in the section titled "D. Parameters in the Public Health Outcomes Module: Evidence and Specification".

6. Modeling Conventions

The probability distributions of specific outcomes are used to compute the numbers of persons with each outcome based on the number of people who become ill. Thus the initial case-outcome probability statement, Pr(physician visit| ill), is consistent with the corresponding state variable, the number of people ill from exposure to the specified dose of SE, in that only those who become ill from a specific dose of SE are considered in the group for whom there is a probability distribution of being seen by a physician.

The numbers of persons with each of the four mutually exclusive outcomes shown above are modeled as binomial distributions using the normal approximation (normal or Gaussian distribution) for the binomial distribution where the mean and standard deviation parameters of the normal distribution are estimated from the binomial parameters n and p:

mean = np

standard deviation = $(npq)^{½}$ where $q = 1-p$.

In each computation n = number of persons in the appropriate state and p = pr(specific outcome from that state) as derived above. Note that both n and p are distributions which are either specified as implicit parameters or are derived as implicit parameters or are derived as parameters of functions or other state variables. Thus the resulting distributions, which are normal distributions with mean = np and std. dev. = $(npq)^{½}$ **,** will not necessarily appear to be normally distributed despite the fact that the resulting distributions are specified as normal distributions in the module. As will be seen in the section titled "F. Outputs of the Public Health Outcomes Module", most state or output variables are log-normally distributed, and this is expected because the distributions of the outputs are derived as <u>products</u> of other distributions.

C. Parameters in the Public Health Outcomes Module: Variables

This section examines in detail the parameters specific to the Public Health Outcomes Module. The paired input distributions of 'dose - number exposed' which are produced by the Preparation and Consumption Module are described in the section of this report titled "Preparation and Consumption Module". The role of the parameters described here can be visualized in Fig. E-2 - Flow Chart of the Public Health Outcomes Module and in Fig E-3. - Outcomes of Illness.

Explicit Parameters

1. **Proportion Susceptible - the proportion of the population which is more susceptible to illness.**

   a. Evidence

   The susceptibility to infection and disease from exposure to any pathogen depends on a complex interaction between the host and the pathogen. Certain sub-populations have been identified which are more susceptible to *Salmonella* as well as other infectious than the general population. A partial list of persons with increased susceptibility to infectious agents includes pregnant women, infants, the elderly, immunocompromised persons (including persons with diabetes, those infected with HIV, inter alia), persons with chronic diseases, nursing home residents, cancer patients, and organ transplant recipients. This group now constitutes nearly 10% of the U.S. population (CAST, 1994.) Recent analysis, which includes more categories of susceptible persons, suggests that the sub-population in the USA which has an increased susceptibility to infections accounts for 20% of the total population (Gerba et al., 1996).

   The elderly are particularly susceptible to infectious agents such as SE for a number of reasons. The disproportionate impact of severe complications and death from salmonellosis in the elderly is illustrated by the epidemiologic evidence:

   (1) 62% of deaths from diarrheal diseases are accounted for by persons over the age of 74 (Lew et al., 1991);

   (2) The case-fatality rate in *Salmonella* outbreaks in nursing homes is 40 times the case-fatality rate for the general population (Levine et al., 1991).

   (3) Acid production in the stomach is recognized as a protective mechanism against ingested pathogens such as SE. However, rates of acid production decline with advancing age, and this places the elderly at further risk.

   There is increasing awareness that the use of antibiotics within 30 days prior to

exposure to *Salmonella* increases susceptibility to *Salmonella* as an enteric pathogen. Oral administration of streptomycin to mice reduced the infectious dose of SE from 10^6 to 10^1 (Bonhoff et al., 1964).

In addition, those persons taking antacids and H2 blockers appear to be at increased risk of salmonellosis because of reduced stomach acidity. Acid production in the stomach is recognized as a protective mechanism against ingested pathogens such as SE.

The observations and evidence above demonstrate that the dose-response relationship found in the data from the feeding trials of different species of *Salmonella* do not accurately represent the likelihood of susceptible individuals developing disease after exposure to *Salmonella* Enteritidis. The available evidence suggests that these susceptible individuals are 10 to 100 times more susceptible to infection, illness, and death from SE than is the general population.

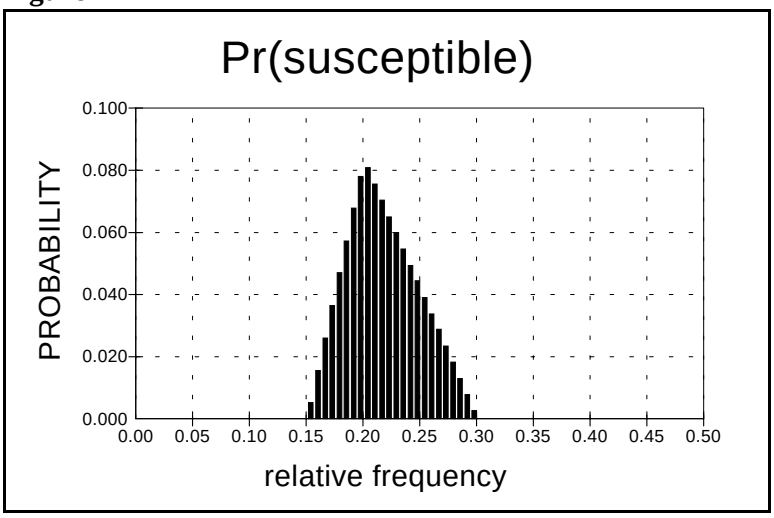
b. Expected Value: 0.22

It is expected that on average, 22% of the population is more susceptible to illness from SE than the normal sub-population.

c. Distribution:[2] Triangular(0.15, 0.20, 0.30)

Mean	0.217
Minimum	0.150
Mode	0.200
Maximum	0.300
$X_{0.05}$	0.184
$X_{0.95}$	0.273

Figure E-4



[2] The distribution for each parameter is described in the syntax of @Risk (the simulation software used to execute this module) in the following general form: DistributionName(parameter 1, parameter 2, etc). For example the triangular distribution has three parameters or arguments, minimum, most likely, and maximum and is specified as "triangular(minimum, most likely, maximum). Statistics include the mean or average value, the mode or most likely value, and the lower and upper 90% confidence limits, the $X_{0.05}$ and $X_{0.95}$ values.

2. Probability Of Physician Visit given Illness, Normal Sub-Population

a. Evidence:

The primary evidence for this parameter comes from the FoodNet active surveillance program carried out by the FDA, USDA, and CDC (CDC, 1997). In the population survey, about 1 in 20 persons who had diarrheal disease reported that they visited a physician for treatment. We used this estimated, 1/20, as the most likely value and estimated minimum and maximum rates by adjusting the numerator by increments of five.

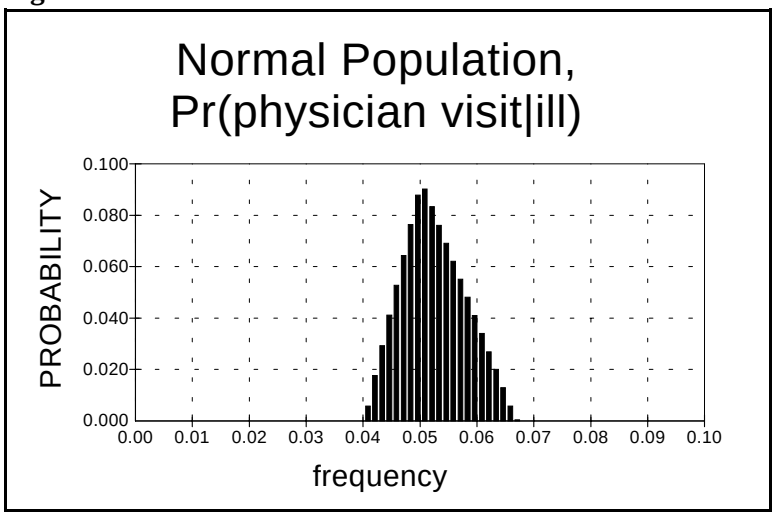
b. Expected Value: 0.0522

It is expected that on average, 522 persons per 10,000 persons in the normal sub-population who become ill from SE will visit a physician.

c. Distribution: Triangular(1/25, 1/20, 1/15)

Mean	0.0522
Minimum	0.0400
Mode	0.0500
Maximum	0.0625
$X_{0.05}$	0.0436
$X_{0.95}$	0.0619

Figure E-5



3. Probability Of Physician Visit Given Illness, Susceptible Sub-Population

a. Evidence:

Clinical and professional experience suggest that susceptible persons are at risk for increased severity and frequency of illness from SE than the normal sub-population, and, therefore, these susceptible persons have a higher probability of seeking medical treatment because of these more severe symptoms and more frequent occurrence of symptoms. In addition, many institutionalized patients and elderly persons in nursing homes will be treated by attending physicians in the institution or nursing home. This may result in an under-reporting of the number of persons seeking care.

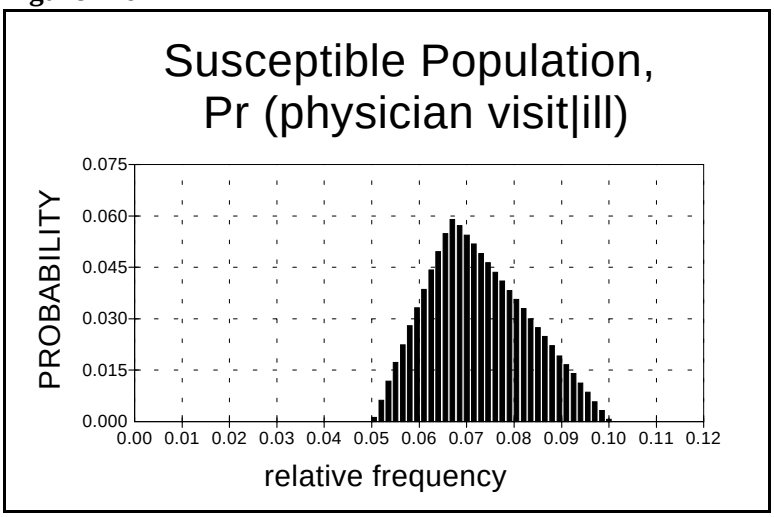
b. Expected Value: 0.0722

It is expected that on average, 722 persons per 10,000 persons in the susceptible sub-population who become ill from SE will visit a physician.

c. Distribution: Triangular(1/20. 1/15, 1/10)

Mean	0.0522
Minimum	0.0500
Mode	0.0667
Maximum	0.1000
$X_{0.05}$	0.0564
$X_{0.95}$	0.0909

Figure E-6



4. Probability Of Being Hospitalized Given Physician Visit, Normal Sub-Population.

a. Evidence: Clinical and professional experience.

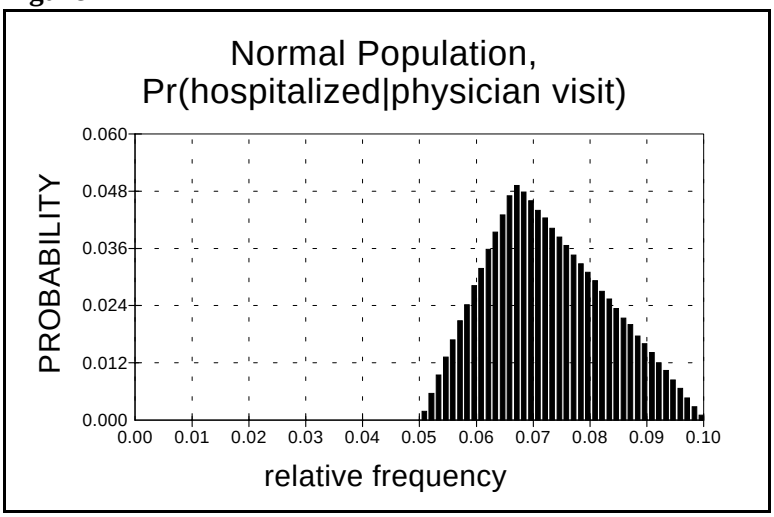
b. Expected Value: 0.0722

It is expected that on average, 722 persons per 10,000 persons in the normal sub-population who become ill from SE and who visit a physician, will be hospitalized.

c. Distribution: Triangular(1/20, 1/15, 1/10)

Mean	0.0722
Minimum	0.0500
Mode	0.0667
Maximum	0.1000
$X_{0.05}$	0.0564
$X_{0.95}$	0.0909

Figure E-7



5. Probability Of Being Hospitalized Given Physician Visit, Susceptible Sub-Population

a. Evidence: Clinical and professional experience. Additional evidence from literature of more severe symptoms in susceptible persons and increased likelihood of hospitalization to treat these conditions.

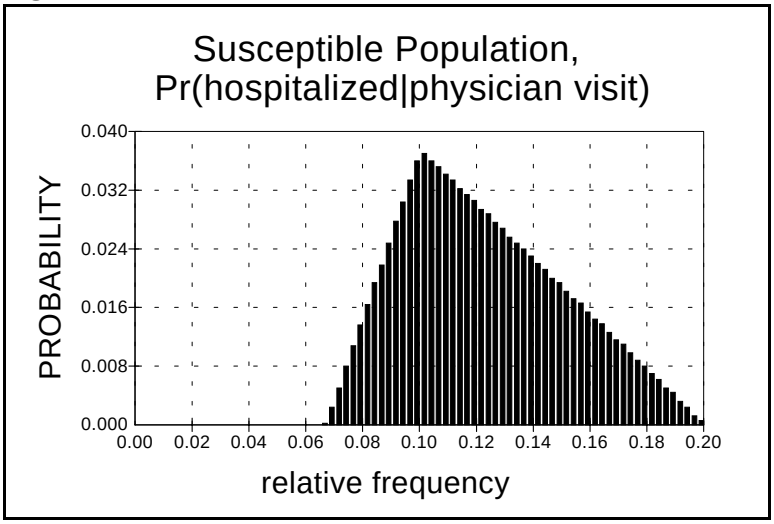
b. Expected Value: 0.1220

It is expected that on average, 1220 persons per 10,000 persons in the susceptible sub-population who become ill from SE and who visit a physician, will be hospitalized.

c. Distribution: Triangular(1/15, 1/10, 1/4)

Mean	0.1220
Minimum	0.0667
Mode	0.1000
Maximum	0.2500
$X_{0.05}$	0.0816
$X_{0.95}$	0.1740

Figure E-8



6. Probability Of Death Given that the Patient is Hospitalized, Normal Sub-Population.

a. Evidence: Clinical and professional experience.

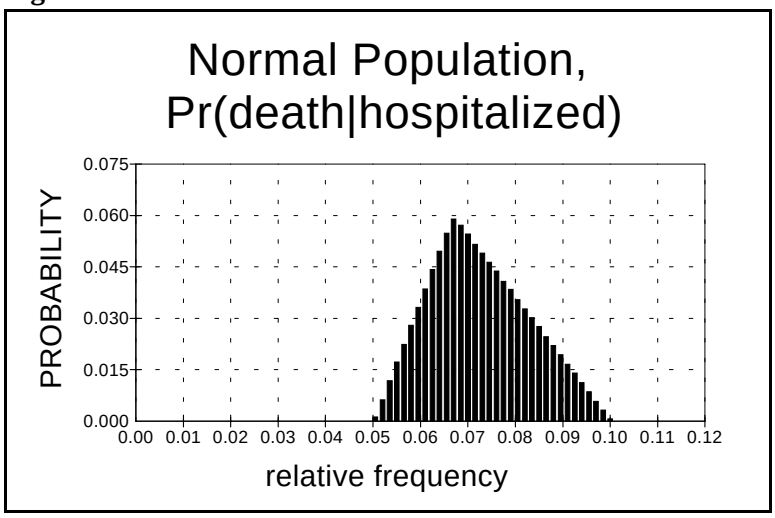
b. Expected value: 0.0722

It is expected that on average, 722 persons per 10,000 persons in the normal sub-population who become ill from SE and who visit a physician and who are hospitalized, will die.

c. Distribution: Triangular(1/20, 1/15, 1/10)

Mean	0.0722
Minimum	0.0500
Mode	0.0667
Maximum	0.1000
$X_{0.05}$	0.0565
$X_{0.95}$	0.0909

Figure E-9



Public Health Outcomes Module

7. Probability Of Death Given Patient Hospitalized, Susceptible Sub-Population.

a. Evidence:

Clinical and professional experience. Published evidence includes reports of case fatality rates in nursing home outbreaks of SE gastroenteritis are 40 times higher than the case fatality rates reported for outbreaks of SE gastroenteritis in general population. In addition, high case fatality rates are reported for severely immunocompromised persons such as those with advanced AIDS and persons undergoing organ transplants**.**

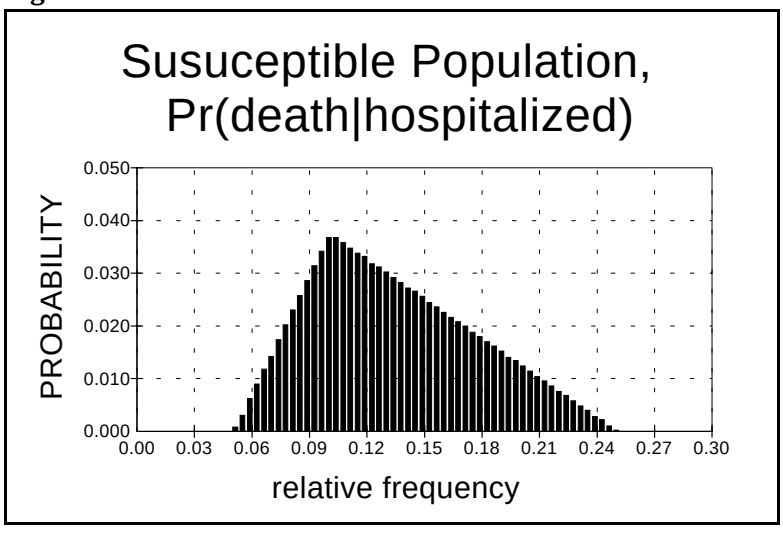
b. Expected value: 0.133

It is expected that on average, 1330 persons per 10,000 persons in the susceptible sub-population who become ill from SE and who visit a physician and who are hospitalized, will die from the SE infection.

c. Distribution: Triangular(1/20, 1/15, 1/4)

Mean	0.1333
Minimum	0.0500
Mode	0.0667
Maximum	0.2500
$X_{0.05}$	0.0723
$X_{0.95}$	0.2112

Figure E-10



8. Probability Of Developing Reactive Arthritis As A Post-Illness Sequela, Normal And Susceptible Sub-Populations.

a. Evidence: Published reports estimate that 2-3% of persons infected with SE and a few other enteric pathogens develop reactive arthritis as a sequela to the infection (CAST, 1994).

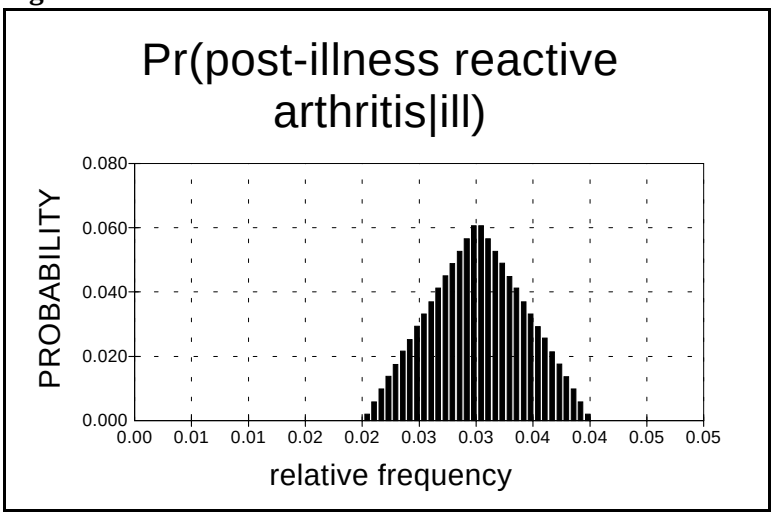
b. Expected value: 0.0300

It is expected that on the average, 300 persons per 10,000 persons in the total population who become ill from SE, will experience joint pain sometime after the recovery from the diarrhea of SE-induce gastroenteritis. This arthritis is called 'reactive arthritis'.

c. Distribution Triangular(0.02,0.03,0.04)

Mean	0.0300
Minimum	0.0200
Mode	0.0300
Maximum	0.0400
$X_{0.05}$	0.0232
$X_{0.95}$	0.0368

Figure E-11



Implicit Parameters

The implicit parameters are derived directly from the explicit parameters. For this reason the implicit parameters do not have distributions specified in the same way as the explicit parameters. The derivation of these implicit parameters is presented in the section titled "B. Inputs, Parameters, and Variables for the Public Health Outcomes Module"on page 198. The statistics describing the following distributions (mean or expected value, minimum, maximum, mode, 5^{th} and 95^{th} percentiles on the cumulative distribution) are generated by a simulation process and are not entered as arguments in functions which produce a distribution. The evidence for the implicit parameters comes from the explicit parameters from which they are derived.

9. Probability Of Recovery Without Medical Treatment, Normal Sub-Population.

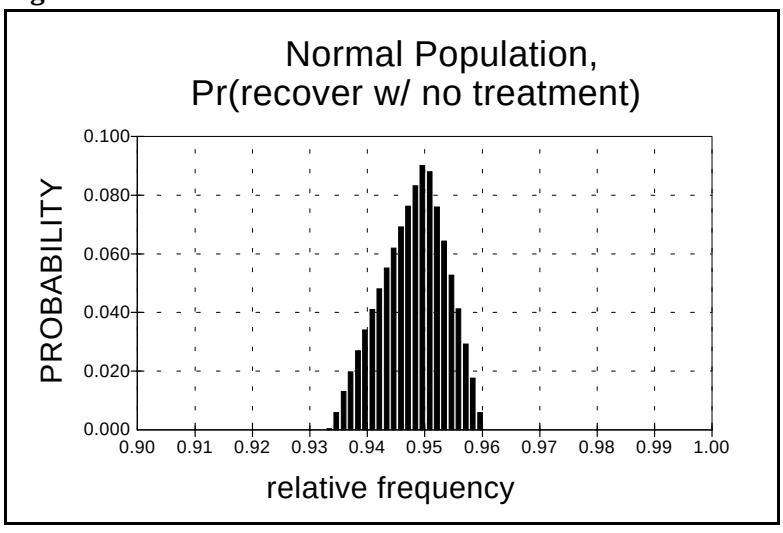
a. Expected value:

It is expected that on average, 9480 persons of 10,000 persons in the normal sub-population who are infected with SE and become ill will recover without seeing a physician.

b. Distribution Statistics:

Mean	0.948
Minimum	0.934
Mode	0.950
Maximum	0.960
$X_{0.05}$	0.938
$X_{0.95}$	0.956

Figure E-12



Public Health Outcomes Module

10. Probability Of Recovery Without Medical Treatment, Susceptible Sub-Population.

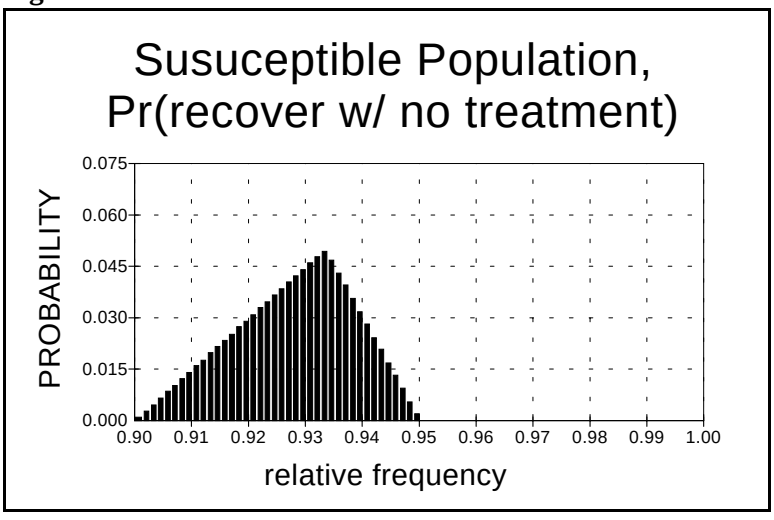
a. Expected value:

It is expected that on average, 9280 persons of 10,000 persons in the susceptible sub-population who are infected with SE and become ill will recover without seeing a physician.

b. Distribution Statistics:

Mean	0.928
Minimum	0.900
Mode	0.933
Maximum	0.950
$X_{0.05}$	0.933
$X_{0.95}$	0.944

Figure E-13



11. Probability Of Physician Visit And Recovery Without Hospitalization, Normal Sub-Population.

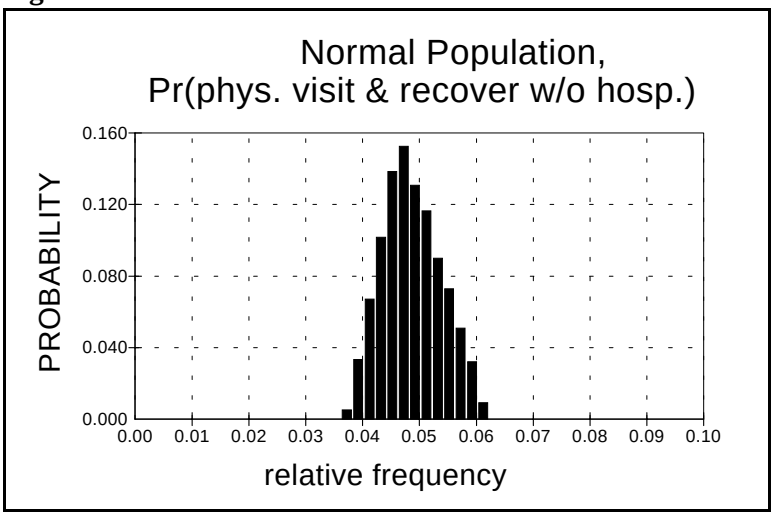
a. Expected value:

It is expected that on average, 485 persons of 10,000 persons in the normal sub-population who are infected with SE and become ill, will see a physician and will recover without being hospitalized.

b. Distribution Statistics:

Mean	0.0485
Minimum	0.0364
Mode	0.0480
Maximum	0.0629
$X_{0.05}$	0.0405
$X_{0.95}$	0.0576

Figure E-14



12. **Probability Of Physician Visit And Recovery Without Hospitalization, Susceptible Sub-Population**.

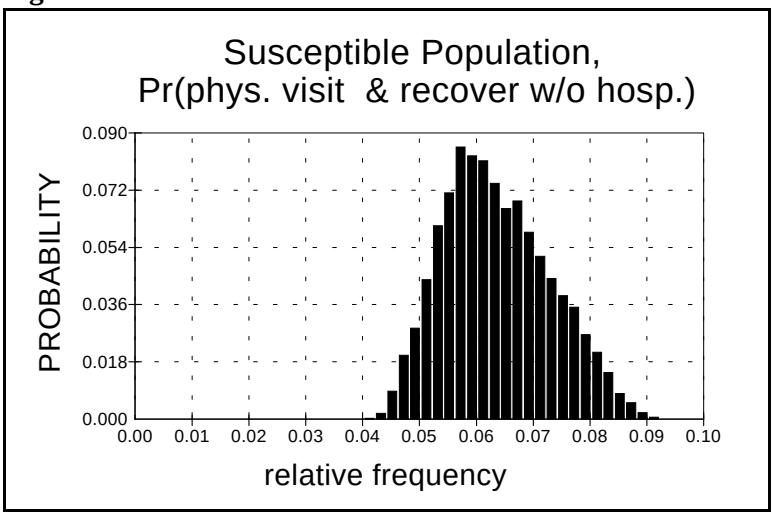
a. Expected value:

It is expected that on average, 634 persons of 10,000 persons in the susceptible sub-population who are infected with SE and become ill, will see a physician and will recover without being hospitalized.

b. Distribution Statistics:

Mean	0.0634
Minimum	0.0437
Mode	0.0699
Maximum	0.0911
$X_{0.05}$	0.0492
$X_{0.95}$	0.0802

Figure E-15



Public Health Outcomes Module

13. Probability Of Physician Visit and Recovery After Hospitalization, Normal Sub-Population.

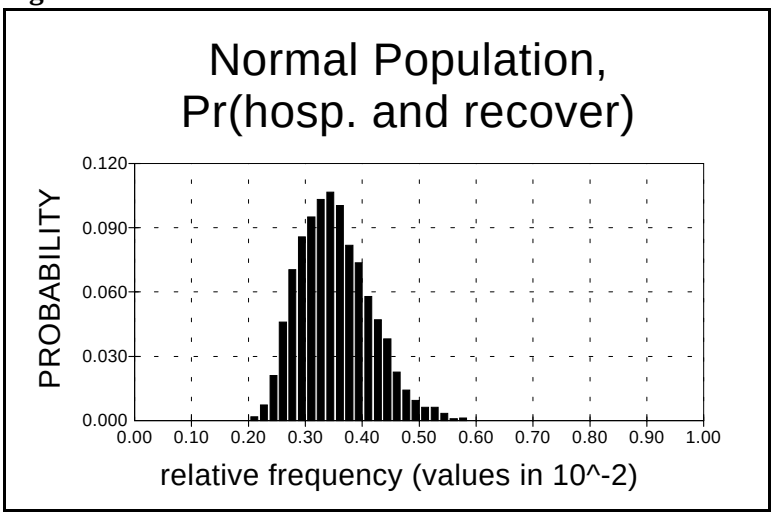
a. Expected value:

It is expected that on average, 35 persons of 10,000 persons in the normal sub-population who are infected with SE and become ill, will see a physician and be hospitalized, and will recover.

b. Distribution Statistics:

Mean	0.00350
Minimum	0.00204
Mode	0.00349
Maximum	0.00596
$X_{0.05}$	0.00256
$X_{0.95}$	0.00462

Figure E-16



Public Health Outcomes Module

14. Probability Of Physician Visit and Recovery After Hospitalization, Susceptible Sub-Population.

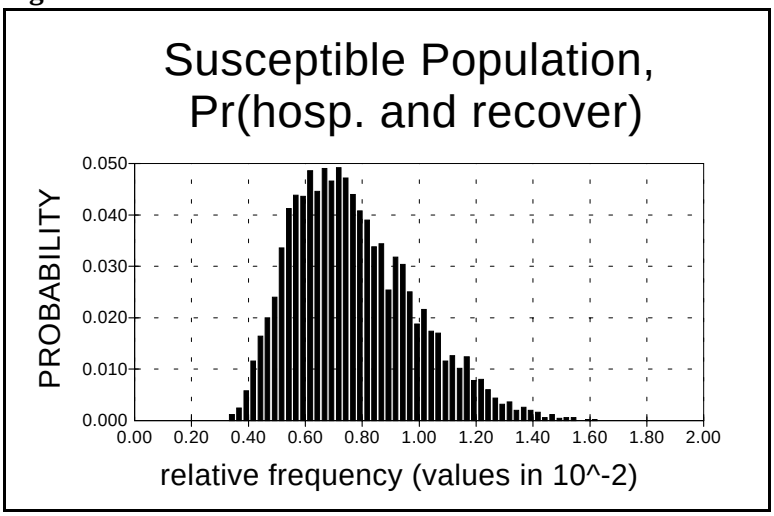
a. Expected value:

It is expected that on average, 77 persons of 10,000 persons in the susceptible sub-population who are infected with SE and become ill, will see a physician and be hospitalized, and will recover.

b. Distribution Statistics:

Mean	0.00765
Minimum	0.00324
Mode	0.00643
Maximum	0.01660
$X_{0.05}$	0.00468
$X_{0.95}$	0.01170

Figure E-17



Public Health Outcomes Module

15. Probability Of Death, Normal Sub-Population.

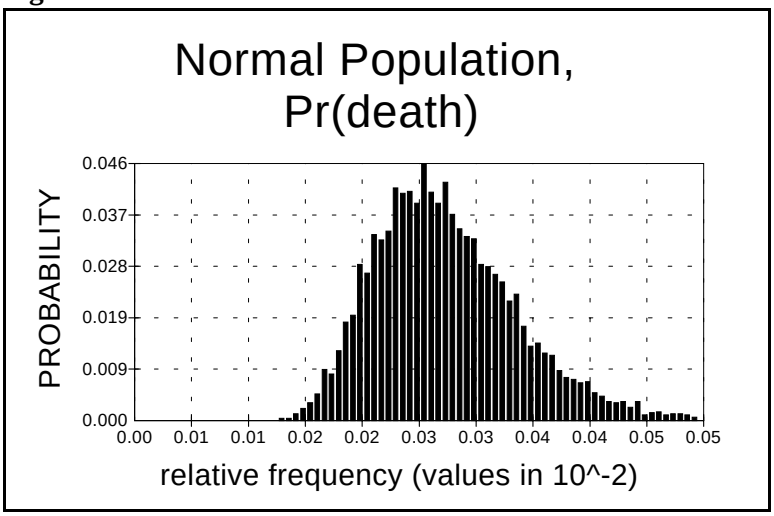
a. Expected value:

It is expected that on average, 3 persons of 10,000 persons in the normal sub-population who are infected with SE and become ill, will see a physician and be hospitalized, and will die.

b. Distribution Statistics:

Mean	0.000272
Minimum	0.000127
Mode	0.000254
Maximum	0.000553
$X_{0.05}$	0.000184
$X_{0.95}$	0.000385

Figure E-18



Public Health Outcomes Module

16. Probability Of Death, Susceptible Sub-Population.

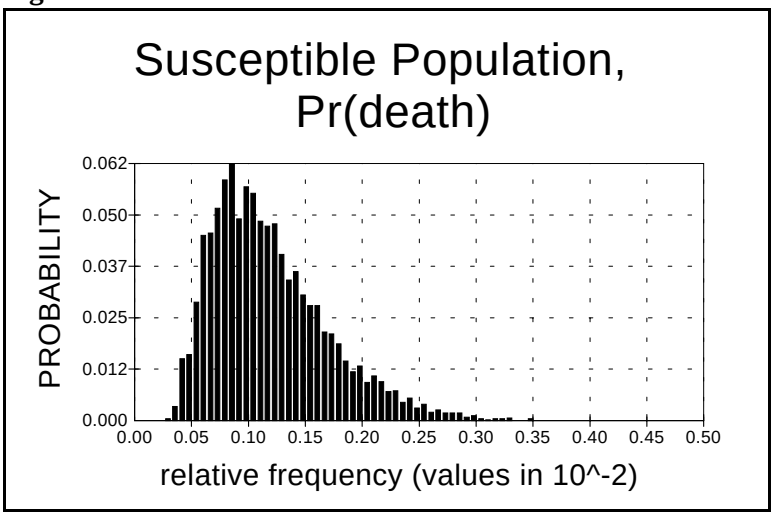
a. Expected value:

It is expected that on average, 11 persons of 10,000 persons in the susceptible sub-population who are infected with SE and become ill, will see a physician and be hospitalized, and will die.

b. Distribution Statistics:

Mean	0.001180
Minimum	0.000248
Mode	0.000783
Maximum	0.003870
$X_{0.05}$	0.000533
$X_{0.95}$	0.002160

Figure E-19



D. Probability of Infection: Microbial Dose-Response Modeling

The probability of infection with illness after ingestion of a specific dose of SE bacteria is not established in the literature. There is no feeding trial with SE bacteria in the literature which establishes a dose-response (i.e. illness) relationship for SE bacteria. There is a large volume of associated scientific literature and theoretical considerations upon which a putative dose-response (i.e. illness) relationship for SE bacteria may be built. Because of the importance of the dose-response (i.e. illness) relationship for SE bacteria to the SERA model, this scientific literature is reviewed in this section which is separate from the other sections of the Public Health Outcomes Module which discuss parameters and inputs.

1. Evidence

Because of the ethical issues involved in testing human responses to toxins and pathogens, few trials using human subjects have been conducted in the United States for decades. Thus, dose-response analysis and inference remains one of the most perplexing and pervasive issues in environmental health and risk analysis for a wide variety of microbial agents.

The analysis of dose-response relationships is based on two distinct types of data: (1) feeding trials using human subjects, and (2) epidemiologic data from "natural experiments". Feeding trials are controlled experiments in which healthy volunteers are fed carefully quantitated doses of pathogens, and the response of the healthy volunteers to the exposure is monitored. "Natural experiments" are outbreaks of bacterial food poisoning in which people are accidentally exposed to bacterial pathogens and become ill in sufficiently large numbers that public health authorities conduct an outbreak investigation. A bacterial cause may be identified, and a specific food containing the pathogen may be identified. Dozens of such outbreaks occur annually in the United States, but implicated food is rarely analyzed to determine the number of organisms per gram of food material.

a. Feeding Trials

Feedings trials have been carried out for a variety of bacterial genera, including *Salmonella*, *Shigella*, *Campylobacter*, *E. coli*, and *Listeria*. Nine *Salmonella* feeding trials were conducted between 1930 and 1973. Six of the nine trials used healthy, male prison volunteers. The most extensive *Salmonella* trials were performed by McCullough and Eisele in 1951 and used *Salmonella* serotypes other than *Salmonella* Enteritidis. The overall conclusion of these feeding trials was that infective doses in the range of 10^5 organisms were needed to achieve a substantial probability of infection or illness (McCullough and Eisele, 1951a, 1951b). However, this conclusion has been repudiated by other work and epidemiologic evidence (D'Aoust, 1989). The shortcomings of the *Salmonella* feeding trials have been summarized by Blaser and Newman (1982): (1) the exclusive use of healthy, young, male prisoners; (2) repeat testing of same subjects with the resulting intestinal immunity as a confounding variable; (3)

small sample sizes; (4) failure to determine minimum infective dose; (5) too few subjects at low doses. Specific limitations of the feeding trials are:

- 18 of the 22 tests-doses had less than 6 subjects.
- *Salmonella* serotypes used in feeding trials include Typhimurium, Anatum, Meleagridis, Newport, Derby, Bareilly, Pullorum, Sofia, Bovis, and Typhi. For all non- typhi *Salmonella* tested, the smallest dose administered was greater than 10^4 *Salmonella* bacteria. Eleven of the 15 tests used a minimum dose exceeding 10^5 *Salmonella* bacteria.
- In all the 11 non-*typhi Salmonella* trials, the lowest dose to cause infection was the lowest dose tested.
- In 6 of 15 trials the lowest dose to cause disease was the lowest dose tested (Blaser and Newman, 1982).
- Experimental evidence suggest that retesting or re-challenging subjects with the same pathogen lowers the probability of illness and/or disease for a given dose (Black et al., 1988).
- Repeated exposure to pathogens reduces likelihood of infection and severity of symptoms to individuals in developing countries (Taylor, 1992).

b. Epidemiologic Evidence from Outbreaks

The food vehicle implicated in most foodborne disease outbreaks is often consumed or discarded before clinical symptoms develop in the exposed individuals. As a result, specific food vehicles and causative agents are confirmed in less than half of all outbreaks, and the pathogen is not commonly cultured from the implicated food vehicle. In the few cases where the implicated food vehicle is available and culture of the implicated food vehicle is done, the bacterial pathogen is even less frequently enumerated. *Salmonella* was enumerated in the implicated food vehicle in some outbreaks before 1982 as summarized by Blaser and Newman (1982). From these outbreak studies and other published outbreak studies since 1982, it has become clear that *Salmonella* is infective and capable of producing disease at doses below the minimum dose used in the feeding trials of 1951. Specific outbreak studies which demonstrated that low doses are capable of causing illness include:

- A large *Salmonella* Enteritidis outbreak in Europe from contaminated candy produced clinical symptoms from the ingestion of less than 50 organisms. It is suspected that the fat content of the chocolate had the effect of protecting the *Salmonella* Enteritidis from gastric acidity, and this made a lower dose exposure effective (Greenwood and Hooper, 1983).

- A single *Salmonella* bacterium was capable of causing disease (D'Aoust, 1985).

- An outbreak of salmonellosis from eating contaminated cheese was reported. Quantitative culture of the cheese showed that consumption of 100-500 SE was the infective dose sufficient to cause symptoms. The fat content of the cheese may have the effect of reducing the infective dose of SE (Fontaine et al., 1980).

- Salmonellosis has been reported from the consumption of 60-230 SE bacteria in hamburger. Again, hamburger is a food containing fat. (Woodburn and Strong, 1960).

- An outbreak of foodborne illness due to SE and involving 150 persons was reported by public health officials in Minnesota. The implicated food vehicle was ice cream. Based on an estimate of the attack rate of 6.6% and the volume of ice cream distributed, it was estimated by number calculation that as many as 29,000 persons in Minnesota may have had diarrhea associated with the SE-contaminated ice cream. In this study the researchers cultured 266 unopened containers of the implicated ice cream. Eight of the containers were positive for SE. Phage typing was done for five of the eight samples and all were phage type 8. Concentration in four of the eight samples was determined and the highest enumeration of SE was 6 SE bacteria per 65 gram sample. This quantity was found in two of eight containers which were positive for SE (Hennessy et al., 1996). A recent study by Vought (Vought, 1998) re-analyzing the data from the enumeration of SE in the implicated ice cream suggests an upper limit of 26 organisms per 65 gram serving.

- An outbreak of salmonellosis due to SE was investigated, and the implicated food was hollandaise sauce. An informal quantitation of one sample of the sauce revealed 10^3 SE bacteria per gram. However, the culture was not performed to extinction, and the specimen had been refrigerated for 72 hours after being taken home in a "doggie bag". If two tablespoons of sauce were used, then the exposure would be about 10^4 SE per person. In this outbreak all of the 39 exposed individuals became ill and 20 were hospitalized (Levy et al., 1996; bacterial count data provided by Dr. M. Moody of the DC Commission on Public Health, personal communication).

* In 12 outbreaks of salmonellosis the *Salmonella* was enumerated in the implicated food vehicle. In 10 of the 12 outbreaks less than 1.5×10^5 *Salmonella* were ingested; in 7 of 10 studies less than 500 *Salmonella* were ingested. This dose is four orders of magnitude less than the minimum dose in most *Salmonella* feeding trials (Blaser and Newman, 1982).

The data from these citations are presented in Table E-3 (see page 235) and shown graphically in Fig. E-23 (see page 233). The few outbreaks of foodborne illness due to SE which report data on the concentration of SE present in the implicated food suggest that the infectious dose which resulting in illness is several orders of magnitude lower than (1) the doses reported in the *Salmonella* feeding trials and (2) the doses which are predicted by dose-response models constructed from the *Salmonella* feeding trials.

- The beta-poisson model was fitted to the pooled data from all of the *Salmonella* feeding trials; the resulting model estimates a probability of infection of 0.20 from ingesting 10^4 *Salmonella* bacteria. Because an infectious dose does not necessarily lead to illness, the probability of infection is greater than the probability of illness. It should be noted that *Salmonella* serotypes other than Enteritidis were used in the *Salmonella* feeding trials (Fazil, 1996).

2. Quantifying Dose-Response Relationships

Mathematical estimation of dose-response relationships is analyzed in a probabilistic framework where illness or other consequence is related to dose as an increasing function. This analysis produces a function that can be used in a predictive model. Issues of concern in quantifying the dose-response relationship include selecting an appropriate functional form, modeling specific outcomes (illness or infection as a function of dose), and extrapolating from the data to lower doses. This analysis is further complicated by the absence of a feeding trail done specifically with SE. For this reason an appropriate *Salmonella* species or other bacteria for which feeding trials have been done must be considered as a surrogate for SE.

Functional Form: A number of mathematical functions or models have been investigated and used for developing predictive models for dose-response relationships for pathogens including parasites, viruses, and bacteria (Crockett et al. 1996; Rose et al., 1991; Haas, 1983; Coleman and Marks, 1997; Morales, 1997). These functional forms include the beta-poisson, exponential, log-normal, log-probit, logit, and Gompertz models. Each has its own particular attributes and drawbacks. Thus the selection of an appropriate functional form should include criteria other than statistical measures. Additional criteria are goodness-of-fit measurements, biological plausibility, and consistency with available evidence, especially when working in a sparse data environment (NSF Workshop on "Specifying Probability Distributions With Limited Data", Proceedings forthcoming in Risk Analysis).

A comprehensive analysis of the known *Salmonella* exposure studies was conducted by fitting a variety of functional forms including the beta-poisson model and exponential model by maximum-likelihood estimation using a spreadsheet (Fazil, 1996). In most cases the beta-poisson had substantially better goodness-of-fit characteristics. The probability of illness by the estimated dose-response functions differs substantially from the attack rates observed in outbreaks of diarrhea due to SE-induced gastroenteritis.

However, the confidence intervals for these estimators can be large. In many cases the 95% confidence area for the dose-response curve included nearly the entire range of the data instead of a smaller range around the estimator of interest. A large 95% confidence interval suggests that the data is extremely variable, sparse, or the functional form does not accurately describe the data.

In general the beta-poisson functional form appears to be a better model for diseases due to viruses and bacteria, while the exponential functional form is a better model for diseases due to parasites. The original form of the beta-poisson, as used by Fazil and Hass (1997), has been modified by several authors (Morales et al, 1996; Teunis et al. 1996) to make parameter estimation more efficient. In this modified form the probability of illness is computed as:

$$Pr(\text{infection}) = 1 - (1 + \text{dose}/\beta)^{-\alpha}.$$

- The beta-poisson function fits the data from the *Shigella* feeding trials better than the exponential function (Crockett et al.,1996).

- The beta-poisson function fits all *Salmonella* feeding trial data, considered separately or pooled, better than the exponential function. (Fazil et al., in press).

- The beta-poisson function has the best goodness-of-fit characteristics, followed by the exponential function, then log-normal and logit functions when fitting a dose-response curve to the data from *Salmonella* feeding trials (Morales et al., 1996)

- The exponential functional form is a better functional form for modeling dose-response data for waterborne parasites such as *Giardia (*Rose et al., 1991).

In general, when fitted to the same data, the exponential function produces a much steeper dose-response curve than the beta-poisson function when fitted to the same data. The beta-poisson seems to overcome some of the limitations of the feeding trial design which rely on a restricted set of subjects who are young, healthy, incarcerated men. It has been observed that flatter dose-response curves are typical of tests conducted on a more heterogeneous population (Morgan, 1992).

3. **Suitable Surrogate Organism for *Salmonella* Enteritidis**

There are no known *Salmonella* Enteritidis feeding trials involving human test subjects upon which a dose-response function may be based. The alternative to this absence of data for SE is to select an appropriate surrogate bacteria for which dose-response data is available. The data for all *Salmonella* species used in feeding trials was analyzed by Fazil (1996). None appear to be appropriate because (1) in some trials the exposure dose was given with water and in other trials the exposure dose was given with food, (2) the

Salmonella species used in the feeding trials appear to be less virulent than SE, based on the epidemiologic data. Morales et al (1996) fitted the data from the *Salmonella* species and *Shigella* species feeding trials to several dose-response functional forms and concluded that the *Salmonella* feeding trial data and low-dose extrapolation of the fitted dose-response functions did not adequately model the attack rates found in the epidemiologic investigations of SE outbreaks involving low-dose exposures (<1,000 organisms) to humans. From their analysis of the *Shigella* species feeding trial data, Morales et al. (1996) proposed *Shigella dysenteriae* as a surrogate for SE in modeling the probability of illness.

The beta-poisson functional form was estimated for the *Shigella dysenteriae* [131] feeding trials by Morales et al. (1996). The resulting dose-response curve was found to also fit the epidemiologic data from the 1994 outbreak of SE associated with ice cream in the low dose range. The 1994 outbreak of SE associated with ice cream was found to have a calculated attack rate of 6.6%, and the infectious dose was assumed to be 6 SE bacteria per 65 gram serving of ice cream (Hennessy, 1995).

4. Adapting the Shigella dysenteriae dose-response function to the Public Health module.

a. Dose-Response Function for the Normal and Susceptible Sub-populations

As discussed in the prior section, there is a sub-population consisting of persons who for a variety of reasons are more susceptible to infection. The clinical and laboratory evidence suggests that these persons are from 10 to 100 times more susceptible to infection than normal, healthy people. The beta-poisson fitted to the *Shigella dysenteriae* [131] data (Morales, 1996) was plotted in two formulations: one formulation with the ID_{50} parameter (related to the infectious dose for 50% of the population) as estimated and another formulation with the ID_{50} parameter reduced by a factor of 10 to indicate a possible dose-response function for susceptible people. These curves were then superimposed on the epidemiologic data (Table E-2, see page 198) to illustrate the compatibility of the *Shigella dysenteriae* dose-response curve and the epidemiologic data (Fig. E-24, see page 234).

b. Introducing Uncertainty To The Dose-Response Function.

The beta-poisson dose-response function is typically expressed with scalar coefficients to produce a deterministic function that computes the probability of illness given an exposure to a specified dose. To make this relationship stochastic, the ID_{50} parameter of the function was expressed as a probability distribution instead of as a constant. Because the beta-poisson functional form is a two-parameter model, the confidence limits can not be estimated by a simple adjustment of the statistical mean by some numerical adjustment of the variance. Confidence limits to these functions are typically estimated by a bootstrap simulation, and the confidence bounds are determined by identifying the

appropriate outliers. To develop an appropriate distribution, the approximate 95% confidence bounds for the *Shigella dysenteriae* were determined from the beta-poisson dose-response function estimated by Teunis et al. (1996). Because the confidence limits appeared to approximately normally distributed in the range of doses of 1,000 to 10,000 bacteria, those bounds were used as the criterion for the stochastic dose-response function using a normal distribution for the ID_{50} parameter. The variance in the distribution (using the estimated ID_{50} parameter as the mean) was iteratively increased until a 95% confidence interval around the probability of illness at a dose of 10^4 organisms was achieved and matched that determined by Teunis et al. (1996).

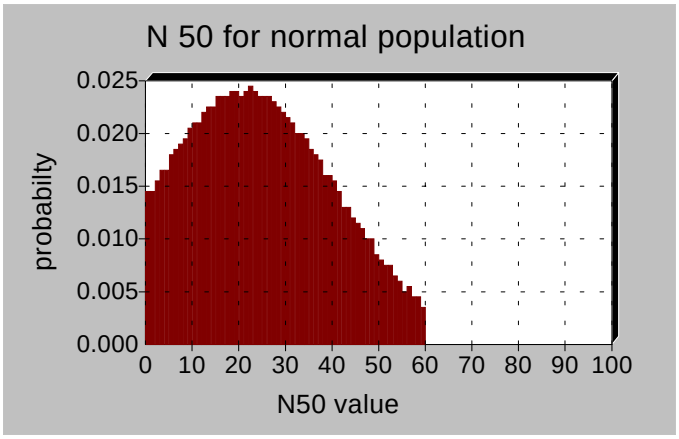
The distribution was then specified as a normal distribution truncated at zero as a minimum to avoid generating negative values which creates an error in the dose-response calculation. This distribution was used for the normal sub-population. For the susceptible sub-population, that sub-population was assumed to at least 10 times as sensitive as the normal sub-population so the distribution parameters were divided by ten.

(1) ID_{50} parameter for the normal sub-population.

Distribution: Truncated normal

Mean = 21.57
Variance = 20,
Minimum = 0
Maximum = 60

Figure E-20

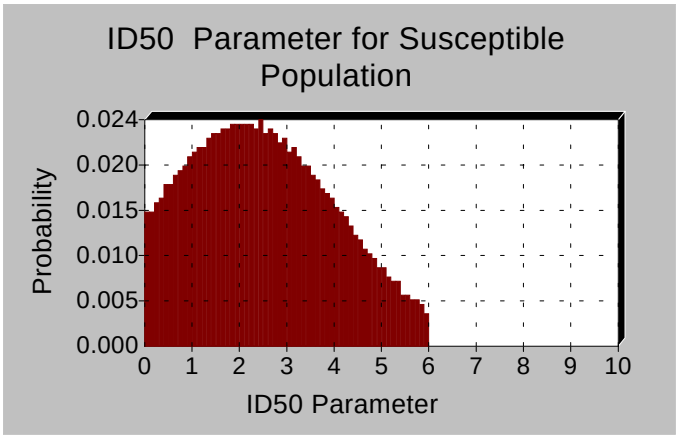


(2) ID_{50} parameter for the susceptible sub-population

Distribution: Truncated normal

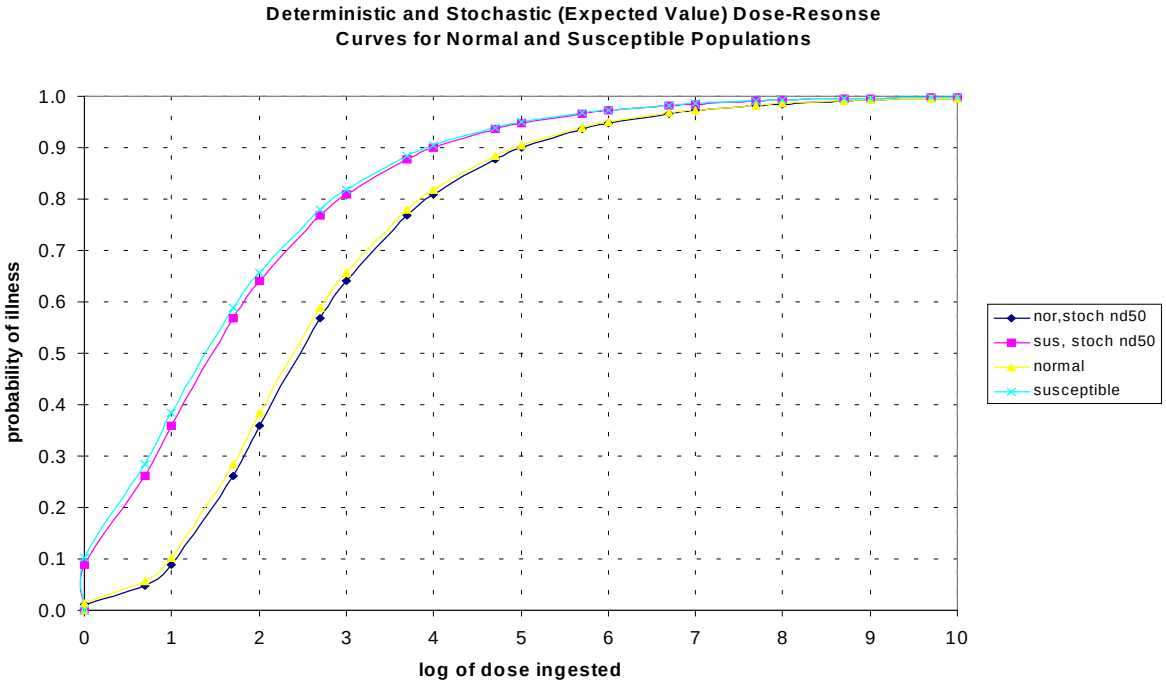
Mean = 2.1157
Std. Dev. = 2.0
Minimum = 0
maximum = 6

Figure E-21



The means of the resulting distributions are slightly different from the specified mean because the distribution is truncated at zero and at the upper bound of 60 for the normal sub-population and 6 for the susceptible sub-population. This imparts a slight downward bias in the probability of illness compared to the deterministic calculation. The two sets of dose-response curves for the expected value of the probabilistic model and the deterministic calculations are displayed in Fig. E-22. The upward bias is evident, but it is less than 2%.

Figure E-22 Comparison of deterministic and expected value of beta-poisson dose response curves



[1] parameter values for deterministic dose response curves estimates by Morales et al (1996).
Susceptible dose-response curve is based on:

ID_{50} of the susceptible sub-population = (ID_{50} normal sub-population)/10.

Figure E-23 Dose and Attack rate in outbreaks of different *Salmonella* species. See table E-3

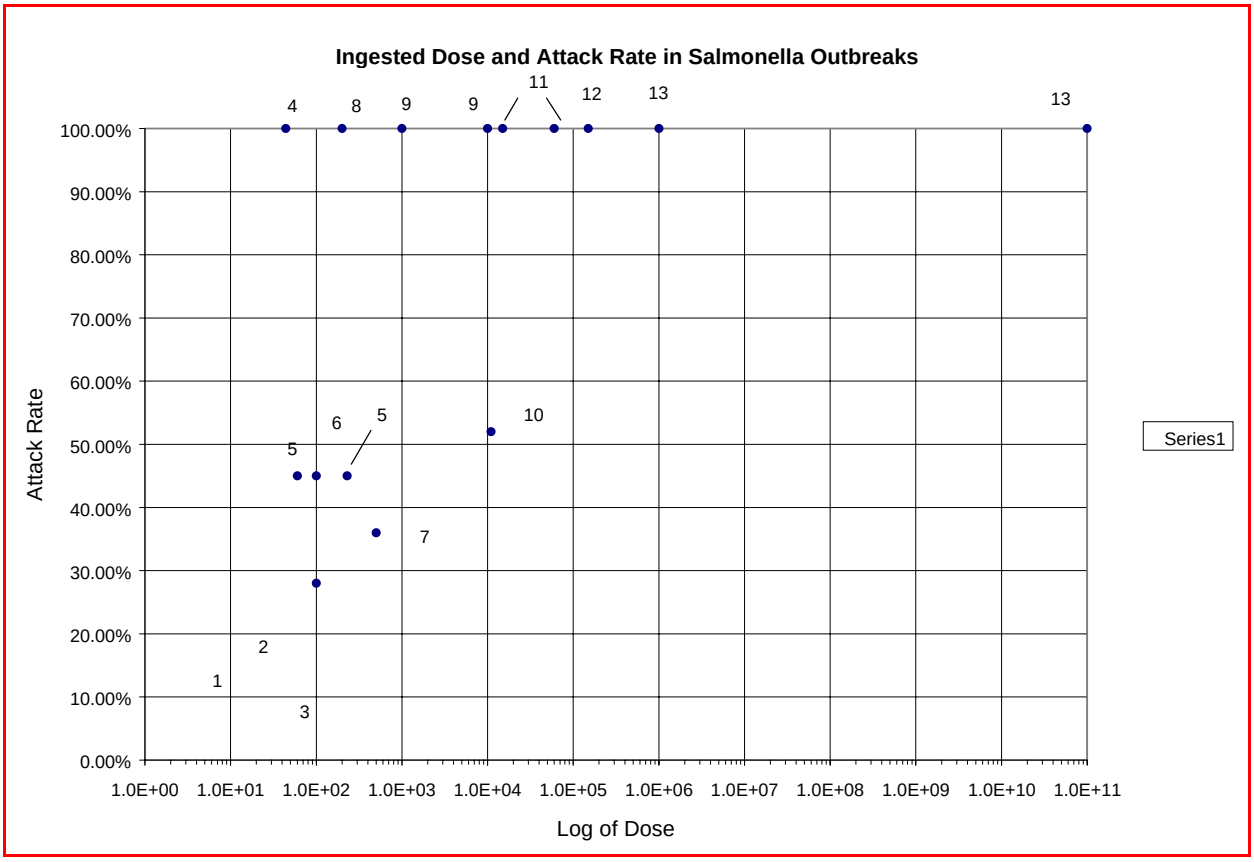


Figure E-24 *Salmonella* outbreak data (ingested dose and attack rate) and beta-poisson dose response curves for *Shigella dysenteriae* estimated for normal and susceptible sub-populations.

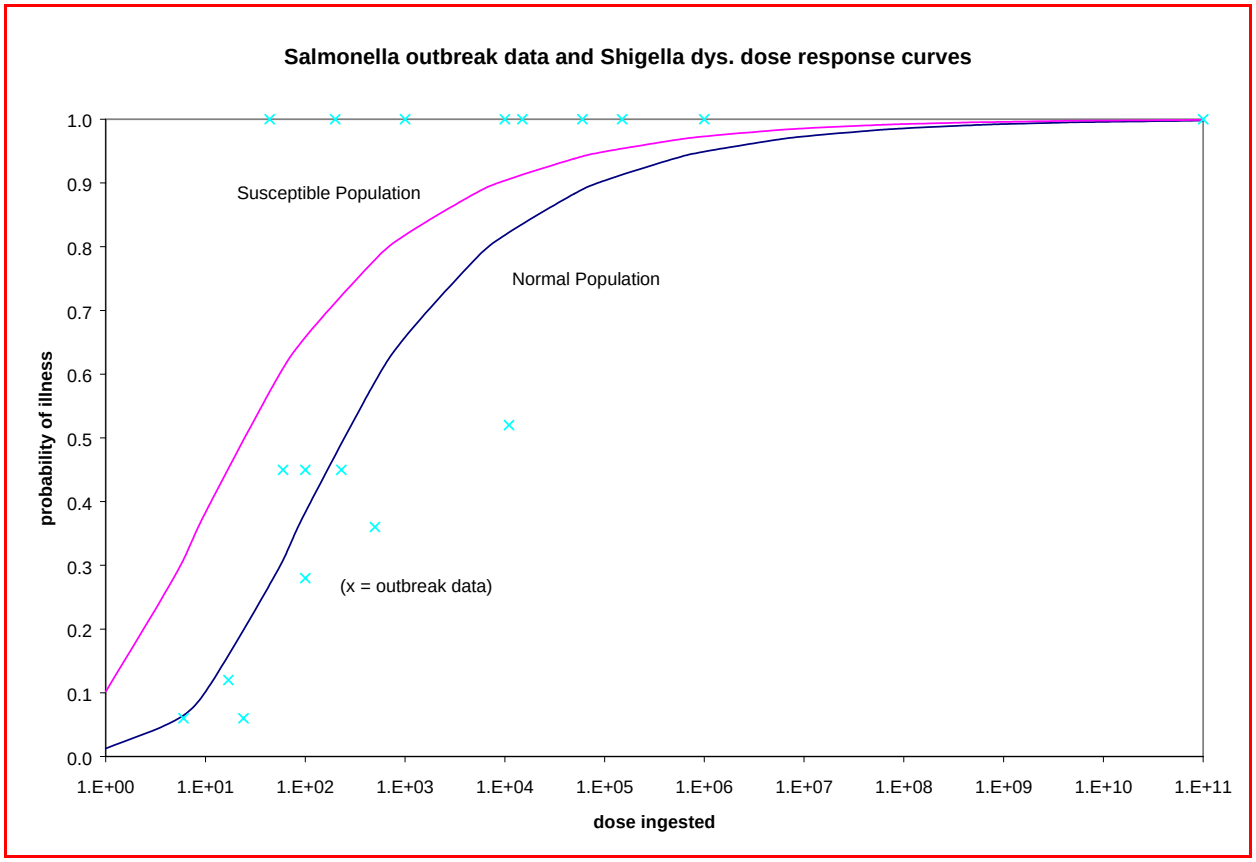


Table E-3. Estimated dose and attack rates in outbreaks of human salmonellosis.

	Serovar	Dose	Log(10) of Dose	Attack Rate	Number Ill	Label number for Fig.E-23 [1]
Boring, J.R. et al.	typhimurium	1.7 x 10	1.23	12%	16,000	2
Lipson, A.	schwarzengrund	44	1.64	100%	1	4
Fontaine, R.E., Arnon, S. et al.	newport	60	1.78	45%	48	5
D'Aoust, J.Y., Aris, B.J., et al.	eastbourne	100	2.00	45%	95	6
Fontaine, R.E., Cohen M.L., et al.	heidelberg	100	2.00	28%	339	7
George, R.H.	heidelberg	200	2.30	100%	1	8
Fontaine, R.E., Arnon, S. et al.	newport	230	2.36	45%	46	5
Fontaine, R.E., Cohen M.L., et al.	heidelberg	500	2.70	36%	339	7
Armstrong, R.W.	typhimurium	11,000	4.04	52%	1,790	10
Lang, D.J., et al.	cubana	15,000	4.18	100%	28	11
Lang, D.J., et al.	cubana	60,000	4.78	100%	28	11
Reitler, R.	zanzibar	150,000	5.18	100%	6	12
Angelotti, R., et al	infantis	1,000,000	6.00	100%	5	13
Reitler, R.	zanzibar	1×10^{11}	11.00	100%	8	12
Hennessy	Enteritidis	6	0.77	6%	>1,000	1
Vought	Enteritidis	24	1.38	6%	>1,000	3
Levy	Enteritidis	1,000	3.00	100%	39	9
Levy	Enteritidis	10,000	4.00	100%	39	9

1. The data for doses and attack rates are shown graphically in Fig. E-23. When two doses are reported for the same study, this indicates that the study reported the exposure dose as a range. Note that the papers by Fontaine, R.E., Arnon, S. et al. and D'Aoust, J.Y., Aris, B.J., et al. did not provide an unambiguous attack rate, and the value of 0.45 was used arbitrarily.

E. Output of the Public Health Outcomes Module

This section describes the typical outputs from the Public Health Outcomes Module as a demonstration of a simulation of a total population 100,000 persons, each ingesting 1,000 SE bacteria. These outputs can be used for validation of the Public Health Outcomes Module, checking the Public Health Outcomes Module for internal consistency, or comparing the results of the Public Health Outcomes Module with other evidence. However, the value of this demonstration simulation for module validation is limited because the number of exposed persons in each sub-population (normal and susceptible) will be different with each simulation. A single simulation run such as this demonstration examines the effects of exposing a total of 100,000 persons to a specific exposure. Readers should note this when examining the number of specific clinical outcomes. In this context a more useful measure for comparing outputs are the rates per 10,000 person exposed or per 10,000 persons who become ill.

Module output is presented graphically in Figs. E-25, E-26, and E-27 (see page 240), and the public health outcomes (number exposed, ill, recover with no treatment, physician visit, hospitalized, death, and reactive arthritis) are illustrated for the normal, susceptible, and total populations, respectively. Summary statistics (mean, minimum, maximum, and the 5^{th} and 95^{th} percentiles of the cumulative distribution) for each group and outcome are presented in Table E-4 (see page 239).

An examination of the graphic output shows all the outputs appear normally distributed on the logarithmic scale; thus all outputs are lognormally distributed. The second feature is the fact that although there is a high probability of illness (averaging 0.65, 0.81, and 0.63 for the normal, susceptible, and total population (Table E-4, see page 239), the vast majority of those ill recover without any medical treatment. The number who are ill is reduced by a 1.5 log reduction to show the number of persons who are ill and being treated by a physician and recovering without being hospitalized. A one log reduction of that group reveals the number of persons who are hospitalized, and a further one log reduction of the hospitalized group shows the number of deaths. In most cases, the uncertainty in the numbers increases as severity of clinical outcome increases. The erratic shape of the curves representing deaths in the normal and total populations and the small blips or tails of the distributions in the normal and susceptible sub-populations (between 3 and 5 logs) are artifacts of the simulation and do not imply any real anomalies.

An interesting feature of the demonstration simulation is the number of cases of reactive arthritis, which is rarely considered in analyzing the impacts of foodborne disease. There are between one-half of a log to one log more cases of persons with reactive arthritis than the number of persons who are hospitalized. This aspect of SE infections in humans may have a more significant clinical and economic impact than previously suspected; many persons suffering from reactive arthritis may not make the connection between a prior episode of gastroenteritis and the delayed onset of reactive arthritis.

The differences in case fatality rates --measure by number deaths/number people ill and deaths per 100,000 ill persons-- suggest (1) the parameter values that influence these numbers should be carefully evaluated and more evidence assembled to improve them, and (2) finding mitigation efforts in this sub-population may have a large impact on reducing mortality from SE infection.

The large uncertainty in the estimates (the 90% confidence limits to the deaths/100,000 susceptible persons are 42.3 persons and 230.2 persons) further indicate the need to refine the parameter values that influence this particular outcome. In general, the estimates for the total population are consistent with case fatality rates previously recorded (CAST, 1994).

The reader should note these results are not the public health outcome of the SE risk assessment; Table E-4 (see page 239) shows the results of a single exposure-dose and do not reflect the other exposures that occur. A full description of the complete public health outcomes is contained in the section containing baseline results.

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Public Health Outcomes Module

Table E-4 Summary statistics for public health outcomes for normal, susceptible, and total populations from the baseline simulation of 100,000 total population exposed to 1,000 SE organisms.

	Statistic				
Population Category and Outcome	Mean	Minimum	Maximum	5 th % *	95 th % *
Normal Sub-Population					
Pr(illness)	0.65	0.55	0.98	0.57	0.79
Ill	78,333	70,106	84,882	72,733	83,601
Exposed	54,548	39,732	77,616	43,655	62,698
Recover, no treatment	48,856	37,445	73,804	41,349	59,180
Physician visit, recover	2,497	1,571	4,221	1,922	3,123
Physician visit, hospitalized, recover	180	69	391	121	254
Death	14	0	42	6	23
Reactive Arthritis	1,546	861	2,782	1,123	2,047
No. Deaths / No. Ill	2.7E-04	0.0E+00	6.9E-04	1.3E-04	4.4E-04
Deaths per 100,000 ill	27.0	0.0	69.0	12.3	44.2
Susceptible Sub-Population					
Pr(illness)	0.82	0.76	0.98	0.77	0.89
Ill	21,677	15,118	29,894	16,934	27,256
Exposed	17,223	11,762	26,494	13,706	22,540
Recover, no treatment	16,443	10,769	24,329	12,700	20,927
Physician visit, recover	1,113	563	2,073	771	1,566
Physician visit, hospitalized, recover	136	35	368	74	218
Death	21	0	78	7	40
Reactive Arthritis	531	240	1,061	369	732
No. Deaths / No. Ill	1.2E-03	0.0E-00	3.4E-03	4.2E-04	2.3E-03
Deaths per 100,000 ill	118	0.0	383	42.4	230.2
Total Population					
Ill	69,270	58,931	93,990	61,890	79,926
Recover, no treatment	65,300	55,132	88,264	58,327	78,426
Physician visit, recover	3,620	2,553	5,844	2,988	4,361
Physician visit, hospitalized, recover	316	171	605	230	417
Death	35	4	89	18	56
Reactive Arthritis	2,071	1,309	3,256	1,644	2,573
No. Deaths / No. Ill	5.1E-04	6.0E-05	1.3E-05	2.7E-04	8.1E-04
Deaths per 100,000 ill	50.5	6.0	134.0	26.8	81.3

* 5 th % and 95 th % are the fractiles of the cumulative distribution

Figure E-25

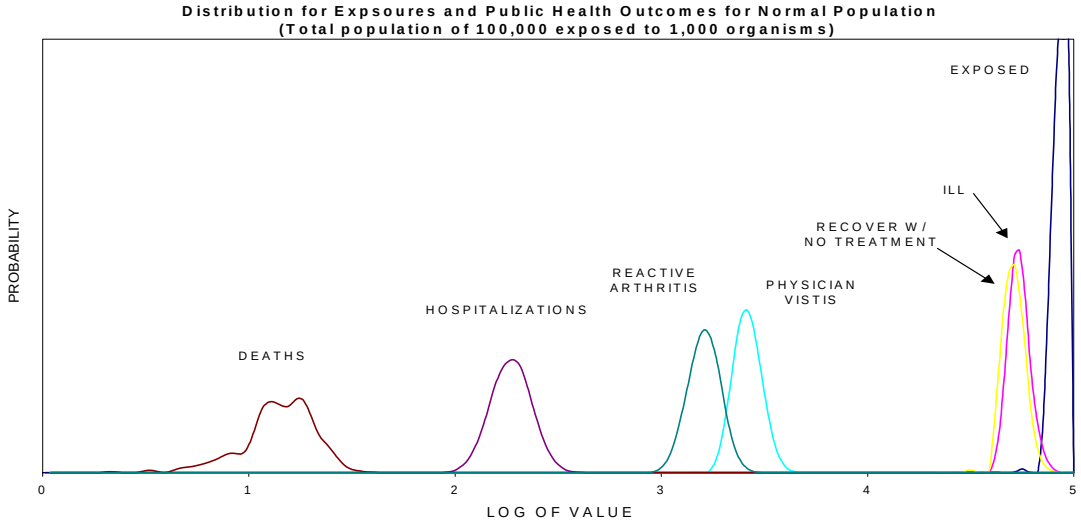


Figure E-26

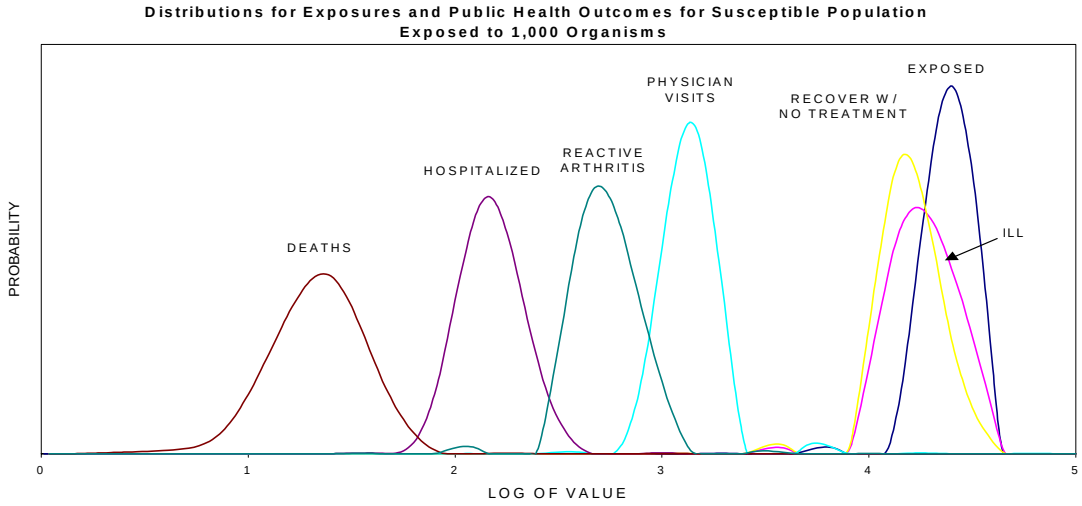
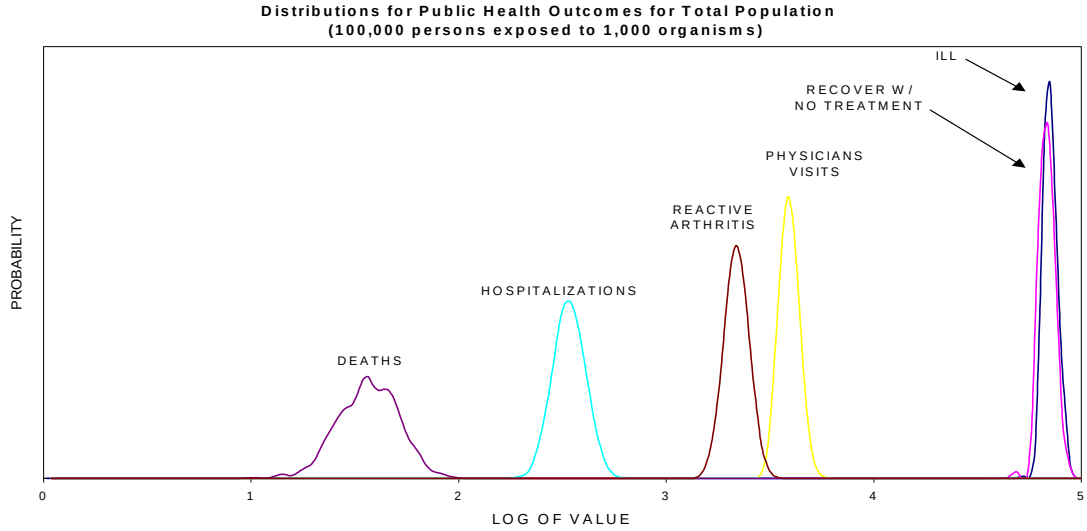


Figure E-27


Distributions for Public Health Outcomes for Total Population
(100,000 persons exposed to 1,000 organisms)
ILL
RECOVER W/
NO TREATMENT
PHYSICIANS
VISITS
REACTIVE
ARTHRITIS
HOSPITALIZATIONS
DEATHS
PROBABILITY
0
1
2
3
4
5
LOG OF VALUE

F. Sensitivity Analysis

1. Purpose

Sensitivity analysis is performed to identify how changes in the parameters of the Public Health Outcomes Module change the values of state or outcome variables. @Risk, the simulation software used in this analysis generates two kinds of sensitivity statistics: (1) regression analysis r^2 values and (2) correlation coefficients. The r^2 values computed for parameters in the Public Health Outcomes Module were all near zero. This indicates a non-linear relationship between the parameters and state variables, and thus the r^2 values are not reported. The rank correlation coefficient is a measure of the degree of association between a parameter and a state or rate variable. Correlation coefficients have values between -1 and +1, inclusive. Negative coefficients indicate the variables are negatively correlated--i.e. a high value for one parameter is associated with a low value in a state or rate variable. The converse is true for positive correlation coefficients, with high value for one variable being correlated to a high value for the other. A rank correlation coefficient approaching zero means little association has been found between a parameter and a variable. A coefficient's absolute value is the measure of the degree of association; the sign indicates a negative or positive correlation.

2. Results

The sensitive analysis results for the demonstration simulation of 100,000 total population with each person exposed to a dose of 1,000 SE bacteria are displayed in Tables E-5 through Table E-10. Tables E-5 to E-7 (see page 244) show the input parameters in the order the input parameters occur in the module. This series of Tables E-5 through E-7 (see page 244) will be most useful for readers seeking to examine the significance of a specific parameter and how it changes between output variables and between normal, susceptible, and total population groups. In Tables E-8 to E-10 (see page 248) the input parameters are listed in descending rank order of correlation. This series of tables will be most useful to the reader seeking to identify the most significant parameters for a specific output variable in the normal, susceptible, or total population groups.

The results shown are specific to the exposure and dose and should not be extrapolated to other doses or exposures. The sensitivity analysis provided for the complete output--the entire range of exposures and doses--will incorporate all the variation and differences in response to different doses. The sensitivity results from the demonstration simulation (100,000 total population each exposed to 1,000 SE bacteria) have value as the correlation coefficients can be examined and analyzed without the complicating factors of other exposures and doses.

A prominent feature of the results for this demonstration simulation is that the significance of a particular parameter varies widely depending on the output. For example, the probability of being in the susceptible sub-population has correlation coefficients ranging from -0.36 to -0.11 for outputs from the normal sub-population (Table E-5, see page 244); yet in the susceptible sub-population, the coefficients are all positive, ranging from +0.28 to +0.95 (Table E-6). For the total population the results are mixed; the coefficients for pr(susceptible) range from -0.09 to +0.77 (Table E-7). In general, for the normal sub-population, all the parameters have significant

effects--with the exception of the outcome for reactive arthritis, only three output-parameter pairs had a correlation with absolute value less than 0.10 and 12 of the 17 output-parameter pairs had coefficients with absolute value greater than 0.25.

The situation is similar for the susceptible sub-population except the pr(susceptible) parameter has more influence, as would be expected. Those parameters with coefficients with absolute value greater than 0.5 include Pr(susceptible), Pr(physician visit), Pr(hosp.|physician visit), and Pr(death|hospitalized). Thus the parameters relating to susceptibility and the probability of clinical outcomes have a larger influence on outcome variables than does the parameter relating to probability of illness, the ID_{50} parameter.

When the outcomes for the susceptible sub-population and the normal sub-population are combined into the total, some of the effects which were quite noticeable in the susceptible sub-population or in the normal sub-population statistics are dampened in the total population outcomes while others emerge as more powerful. For example, the ID_{50} parameters for both the normal sub-population and susceptible sub-population range from -0.11 to -0.97, but in general are quite high, indicating that this parameter is one of the most important in terms of its effect on the outcome values (Table E-7).

When the input parameters are listed by their rank order (in descending order of absolute value of the correlation coefficient), the relative significance of specific parameters for either a specific output or between outputs is more clear. As one would expect, the most significant parameter for each output is the one most closely related to it, e.g., in the normal sub-population, for the number of persons seeing physician and recovering (without being hospitalized), the most significant parameter is pr(hosp|physician visit) (Table E-8, see page 248). In general, as a parameter is further distanced from an output in terms of the illness to clinical outcomes continuum, its correlation coefficient (absolute value) declines. The ID_{50} parameters for the normal sub-population and susceptible sub-population have high rank order for total ill, number recovering without treatment, and number seeing physician and recovering. The ID_{50} parameters begin to decline to where they are last in rank order for the number of deaths (Table E-10). An inspection of the tables will reveal there are no unimportant variables, e.g., those with consistently low rank correlation; they are all significant to one or more output variables.

Table E-5. Sensitivity Analysis for Normal Sub-Population Outputs

Output Variable	Input Parameter	Correlation Coefficient
Number recover with no treatment	Pr(susceptible)	-0.367372
	NP: ID50 parameter	-0.918353
	NP: Pr(physician visit)	-6.16E-02
number physician visit and recover	Pr(susceptible)	-0.250138
	NP: ID50 parameter	-0.628577
	NP: Pr(physician visit)	+0.680765
	NP: Pr(hosp.|phys vis)	-8.15E-02
number hospitalized and recover	Pr(susceptible)	-0.162457
	NP: ID50 parameter	-0.424199
	NP: Pr(physician visit)	+0.458259
	NP: Pr(hosp.|phys. visit)	+0.637448
	NP: Pr(death|hosp.)	-6.14E-02
number deaths	Pr(susceptible)	-0.106447
	NP: ID50 parameter	-0.250416
	NP: Pr(physician visit)	+0.269777
	NP: Pr(hosp.|phys. visit)	+0.369393
	NP: Pr(death|hosp.)	+0.364551
cases of reactive arthritis	Pr(susceptible)	-0.228819
	NP: ID50 parameter	-0.549129
	NP: Pr(physician visit)	-1.38E-02
	NP: Pr(hosp.|phys. visit	-1.25E-02
	NP: Pr(death|hosp.)	+1.04E-03
	NP: Pr(reactive arthritis)	+0.773724

Table E-6. Sensitivity Analysis for Susceptible Sub-Population Outputs

Output Variable	Input Parameter	Correlation Coefficient
total ill	Pr(susceptible)	
	SP: ID50 parameter	
number recover with no treatment	Pr(susceptible)	+0.952977
	SP: ID50 parameter	-0.282389
	SP: Pr(physician visit)	-4.23E-02
number physician visits and recover	Pr(susceptible)	+0.770726
	SP: ID50 parameter	-0.232542
	SP: Pr(physician visit)	+0.525231
	SP: Pr(hosp.|phys vis)	-0.173962
number hospitalized and recover	Pr(susceptible)	+0.460219
	SP: ID50 parameter	-0.137337
	SP: Pr(physician visit)	-0.303962
	SP: Pr(hosp.|phys. visit)	+0.740909
	SP: Pr(death|hosp.)	-0.147705
number deaths	Pr(susceptible)	+0.287700
	SP: ID50 parameter	-9.72E-02
	SP: Pr(physician visit)	+0.186787
	SP: Pr(hosp.|phys. visit)	+0.455073
	SP: Pr(death|hosp.)	+0.659489
number cases of reactive arthritis	Pr(susceptible)	+0.681972
	SP: ID50 parameter	-0.193067
	SP: Pr(physician visit)	+5.52E-03
	SP: Pr(hosp.|phys. visit)	-1.31E-04
	SP: Pr(death|hosp.)	-1.89E-04
	SP: Pr(reactive arthritis)	-0.647577

Table E-7. Sensitivity Analysis for Total Population Outputs

Output Variable	Input Parameter	Correlation Coefficient
total ill	Pr(susceptible)	+0.104012
	SP: ID50 parameter	-0.159807
	NP: ID50 parameter	-0.976487
number recover with no treatment	Pr(susceptible)	+0.089920
	SP: ID50 parameter	-0.154922
	SP: Pr(physician visit)	+3.00E-03
	NP: ID50 parameter	-0.976811
	NP: Pr(physician visit)	-6.40E-02
number physician visits and recover	Pr(susceptible)	+0.770726
	SP: ID50 parameter	-0.232542
	SP: Pr(physician visit)	0.525231
	SP: Pr(hosp.|phys vis)	-8.173962
	NP: ID50 parameter	-0.590174
	NP: Pr(physician visit)	+0.638876
	NP: Pr(hosp|phys vis)	-6.45E-02
number hospitalized and recover	Pr(susceptible)	+0.237280
	SP: ID50 parameter	-0.111802
	SP: Pr(physician visit)	+0.232600
	SP: Pr(hosp.|phys. visit)	+0.564520
	SP: Pr(death|hosp.)	-0.117790
	NP: ID50 parameter	-0.297148
	NP: Pr(physician visit)	+0.315010
	NP: Pr(hosp.|phys. visit)	+0.440054
	NP: Pr(death|hosp.)	-3.80E-02

(Table continued on next page)

Table E-7. Sensitivity Analysis for Total Population Outputs, continued

Output Variable	Input Parameter	Correlation Coefficient
number deaths	SP: ID50 parameter	-9.52E-02
	Pr(susceptible)	+0.208832
	SP: Pr(physician visit)	+0.169202
	SP: Pr(hosp.|phys. visit)	+0.408376
	SP: Pr(death|hosp.)	+0.594600
	NP: Pr (physician visit)	+0.129622
	NP: Pr(hosp.|phys. visit)	+0.172914
	NP: Pr(death|hosp.)	+0.165032
	NP: ID50 parameter	-0.113232
number cases of reactive arthritis	Pr(susceptible)	+3.94E-02
	SP: ID50 parameter	-9.35E-02
	SP: Pr(physician visit)	+5.65E-03
	SP: Pr(hosp.|phys. visit)	-8.94E-03
	SP: Pr(death|hosp.)	-7.69E-03
	SP: Pr(reactive arthritis)	+0.249099
	NP: ID50 parameter	-0.543518
	NP: Pr(physician visit)	-9.05E-03
	NP: Pr(hosp.|phys. visit)	-3.52E-03
	NP: Pr(death|hosp.)	-2.88E-03
	NP: Pr(reactive arthritis)	+0.772666

Table E-8. Sensitivity Analysis for Normal Sub-Population: Input Parameters by Rank Order Correlation

Output Variable	Input Parameter	Correlation Coefficient
Number recover with no treatment	NP: ID50 parameter	-0.918353
	Pr(susceptible)	-0.367372
	NP: Pr(physician visit)	-6.16E-02
number physician visit and recover	NP: Pr(physician visit)	+0.680765
	NP: ID50 parameter	-0.628577
	Pr(susceptible)	-0.250138
	NP: Pr(hosp.|phys vis)	-8.15E-02
number hospitalized and recover	NP: Pr(hosp.|phys. visit)	+0.637448
	NP: Pr(physician visit)	+0.458259
	NP: ID50 parameter	-0.424199
	Pr(susceptible)	-0.162457
	NP: Pr(death|hosp.)	-6.14E-02
number deaths	NP: Pr(hosp.|phys. visit)	+0.369393
	NP: Pr(death|hosp.)	+0.364551
	NP: Pr(physician visit)	+0.269777
	NP: ID50 parameter	-0.250416
	Pr(susceptible)	-0.106447
cases of reactive arthritis	NP: Pr(reactive arthritis)	+0.773724
	NP: ID50 parameter	-0.549129
	Pr(susceptible)	-0.228819
	NP: Pr(physician visit)	-1.38E-02
	NP: Pr(hosp.|phys. visit)	-1.25E-02
	NP: Pr(death|hosp.)	+1.04E-03

Table E-9. Sensitivity Analysis for Susceptible Sub-Population Outputs: Input Parameters by Rank Order Correlation.

Output Variable	Input Parameter	Correlation Coefficient
number recover	Pr(susceptible)	+0.952977
with no treatment	SP: ID50 parameter	-0.282389
	SP: Pr(physician visit)	-4.23E-02
number physician	Pr(susceptible)	+0.770726
visits and recover	SP: Pr(physician visit)	+0.525231
	SP: ID50 parameter	-0.232542
	SP: Pr(hosp.|phys visit)	-0.173962
number hospitalized	SP: Pr(hosp.|phys. visit)	+0.740909
and recover	Pr(susceptible)	+0.460219
	SP: Pr(physician visit)	-0.303962
	SP: Pr(death|hosp.)	-0.147705
	SP: ID50 parameter	-0.137337
number deaths	SP: Pr(death|hosp.)	+0.659489
	SP: Pr(hosp.|phys. visit)	+0.455073
	Pr(susceptible)	+0.287700
	SP: Pr(physician visit)	+0.186787
	SP: ID50 parameter	-9.72E-02
number cases of	Pr(susceptible)	+0.681972
reactive arthritis	SP: Pr(reactive arthritis)	+0.647577
	SP: ID50 parameter	-0.193067
	SP: Pr(physician visit)	+5.52E-03
	SP: Pr(death|hosp.)	-1.89E-04
	SP: Pr(hosp.|phys. visit)	-1.31E-04

Table E-10. Sensitivity Analysis for Total Population Outputs: Input Parameters by Rank Order Correlation

Output Variable	Input Parameter	Correlation Coefficient
total ill	NP: ID50 parameter	-0.976487
	Pr(susceptible)	+0.104012
	SP: ID50 parameter	-0.159807
number recover with no treatment	NP: ID50 parameter	-0.976811
	SP: ID50 parameter	-0.154922
	Pr(susceptible)	+0.089920
	NP: Pr(physician visit)	-6.40E-02
	SP: Pr(physician visit)	+3.00E-03
number physician visits and recover	Pr(susceptible)	+0.770726
	NP: Pr(physician visit)	+0.638876
	NP: ID50 parameter	-0.590174
	SP: Pr(physician visit)	+ 0.525231
	SP: ID50 parameter	-0.232542
	SP: Pr(hosp.|phys. visit)	-8.173962
	NP: Pr(hosp.|phys. visit)	-6.45E-02
number hospitalized and recover	SP: Pr(hosp.|phys. visit)	+0.564520
	NP: Pr(hosp.|phys. visit)	+0.440054
	NP: Pr(physician visit)	+0.315010
	NP: ID50 parameter	-0.297148
	Pr(susceptible)	+0.237280
	SP: Pr(physician visit)	+0.232600
	SP: Pr(death|hosp.)	-0.117790
	SP: ID50 parameter	-0.111802
	NP: Pr(death|hosp.)	-3.80E-02

(Table continued on next page)

Table E-10. Sensitivity Analysis for Total Population Outputs: Input Parameters by Rank Order Correlation, continued

Output Variable	Input Parameter	Correlation Coefficient
number deaths	SP: Pr(death|hosp.)	+0.594600
	SP: Pr(hosp.|phys. visit)	+0.408376
	Pr(susceptible)	+0.208832
	NP: Pr(hosp.|phys. visit)	+0.172914
	NP: Pr(death|hosp.)	+0.165032
	SP: Pr(physician visit)	+0.169202
	NP: Pr (physician visit)	+0.129622
	NP: ID50 parameter	-0.113232
	SP: ID50 parameter	-9.52E-02
number cases of reactive arthritis	NP: Pr(reactive arthritis)	+0.772666
	NP: ID50 parameter	-0.543518
	SP: Pr(reactive arthritis)	+0.249099
	SP: ID50 parameter	-9.35E-02
	Pr(susceptible)	+3.94E-02
	Pr(susceptible)	+3.94E-02
	SP: Pr(hosp.|phys. visit)	-8.94E-03
	SP: Pr(death|hosp.)	-7.69E-03
	SP: Pr(physician visit)	+5.65E-03
	NP: Pr(hosp.|phys. visit)	-3.52E-03
	NP: Pr(death|hosp.)	-2.88E-03

G. Limitations

1. Model Parameters.

a. Proportion susceptible.

Although several sources identify and quantify the types and numbers of persons who are deemed to be more susceptible to foodborne pathogens (Gerba, 1994; CAST, 1994), these data have several limitations. Among the susceptible sub-population there is a large range of susceptibility to pathogens, and there are significant differences in the probability of specific clinical outcomes among the susceptible sub-population. For example, the probability of death after the onset of illness (i.e. Pr(death|ill)) for nursing home residents involved in *Salmonella* outbreaks is 70 times higher than the overall case-fatality rate in outbreaks of salmonellosis in the general population (Mishu et al. 1994). The probability of specific clinical outcomes for the most robust of the susceptible group may be nearly that of the most susceptible person in the normal sub-population. The probability of specific clinical outcomes could be modeled more accurately by further stratifying the susceptible sub-population. In addition, we have no information about the disease avoidance behaviors, which may be unique to the susceptible sub-population, and we have no information about the prevalence of such behaviors among the susceptible sub-population.

b. Dose-Response Parameters (probability of illness)

The calculation of the probability of illness after exposure to a specific dose has several limitations.

(1) The most significant limitation is the absence in the literature of a feeding trial in which SE is the bacteria being studied with the intention of describing a dose- response relationship.

(2) Limitations of data from feeding trials of enteric pathogens.

The section titled “C. Parameters in the Public Health Outcomes Module: Variables” (see page 206) details the limitations of the data from the feeding trial studies on enteric pathogens. Among the shortcomings of these studies are the small sample sizes at each dose-exposure level, the repeated use of the same subjects in the same feeding trial, the absence of exposure of test subjects to low doses of the enteric pathogen, and the use of minimum doses which were relatively large in most trials. Furthermore, large differences were observed between strains of specific serovars. These large differences make it difficult to extrapolate from the results of strains used in the feeding trial studies to exposure of humans to different strains not used in the feeding trial studies. These large differences produce a dose-response curve which

has very wide 95% confidence interval curves around the dose-response curve which has been fitted to the data form the appropriate feeding trials. The consequence of these large differences is to limit our confidence in the expected values which are generated from the dose-response curves of the feeding trial studies.

(3) Functional form for expressing dose-response relationships.

Combined with the data limitations of the feeding trials, it is not obvious which of the mathematical functional forms best characterizes the dose-response relationship between the bacterial enteric pathogens of the feeding trial studies and the population of test subjects in those feeding trials. The appropriate choice of mathematical functional form continues to plague dose-response analysis in bacterial risk assessment. Although the beta-poisson functional form has the best "goodness-of-fit" characteristics, when it is used to model most bacterial pathogens (Crockett, 1995; Fazil, 1997; Hass, 1996; Morales, 1996), several analysts have noted shortcomings in the use of the beta-poisson (Morales, 1996; Vose, 1998) on theoretical grounds as well as in parameter estimation for use in practical applications. Visual inspection of the confidence limits for a typical beta-poisson dose-response function reveals that a wide variety of functional forms will produce dose-response curves which are contained within the confidence limits of the beta-poisson dose-response function. The appropriate functional form for modeling a dose-response relationship for low-dose exposure has not been established. The functional form for modeling a dose-response relationship for low-dose exposure may be different from the functional form for modeling a dose-response relationship for moderate- or high-dose exposure to bacterial pathogens. Finally, there are arguments in the literature for the use of functional forms other than the beta-poisson functional form; it is argued that these other functional forms may better model the probability of illness after exposure (Morales, 1996).

(4) Incorporating uncertainty in calculating probability of illness.

Because the beta-poisson functional form is a two-parameter model, confidence intervals for the beta-poisson functional form are computed by a bootstrap method and are not computed analytically. This requirement to use a bootstrap method of calculation for the confidence interval complicates the explicit specification of uncertainty in dose-response calculations. Thus the uncertainty in dose-response calculations can not be specified by incorporating some numerical multiple of the variance of a particular estimator. Furthermore, the confidence interval around the probability of illness after an exposure to a specific number of organisms is not constant over the range of doses to

which people are exposed in daily life. The practical result of using the beta-poisson functional form is that risk-analysts must resort to the types of approximations we have used in modeling the dose-response relationship with the beta-poisson functional form. Additional research in quantitative methods is needed to remedy this aspect of bacterial risk modeling.

(5) Variation in response to pathogens in different food vehicles and different meal sizes.

It is well established that foods with a high-fat content protect bacteria from the bactericidal effects of gastric acidity. It is also recognized that, when the same number of bacteria are consumed but the total amount of food varies, the amount of food consumed is negatively correlated to probability of illness - i.e. for the same number of bacteria, the more food eaten, then the less likely the risk of diarrhea . Food vehicle and meal size are, therefore, two important variables in predicting the response to exposure to a given number of bacteria. These two factors further complicate the construction of an appropriate dose-response curve.

c. Probability of clinical outcomes when ill.

Several of the parameters which describe the probabilities for clinical outcomes of disease were not described explicitly because of the lack of data. These parameters were derived from other conditional probabilities which were explicitly described based on clinical professional experience.

(1) Probability of seeing a physician, if ill.

The basic source of evidence for this parameter is the FoodNet project results (CDC, 1998). We assumed this value was appropriate for the normal sub-population, but we had no explicit data or survey results to describe the uncertainty around this estimate. We are aware of no published estimate of this parameter for the susceptible sub-populations, and the value of this estimate for the susceptible sub-population will vary widely within the susceptible sub-population depending on their particular health status and underlying medical problems and age.

(2) The other conditional probabilities for both normal and susceptible sub-populations suffer from the same lack of published data or information. Within the susceptible sub-populations, the probability of specific outcomes will vary considerably given the age and medical status of the individual.

(3) There is evidence that the conditional probabilities of specific clinical outcomes for an ill individual is functionally related to the number of organisms ingested.

Evidence suggests that with an increasing dose of the enteric pathogen the incubation period is shorter after exposure and the symptoms are more severe; It is believed that as the ingested dose of the enteric pathogen increases, the probability of a physician visit and subsequent hospitalization increases. Because of lack of data, we did not incorporate this belief into the computation of the probability of specific clinical outcomes. As public health investigators collect more data during outbreak investigations pertaining to the likely numbers of pathogens ingested, ingested dose can be correlated to clinical outcomes, and this correlation can be included in future modeling efforts.

d. Probability of long-term sequelae to illness.

Although a number of to infection with SE have been identified, we estimated the frequency of only one long-term sequelae, and that is reactive arthritis. We are not aware of epidemiologic evidence or data which quantifies the rate of reactive arthritis at different levels of exposure to SE. Such epidemiologic data would be used in validating the results of the model. A complicating factor is the observation that reactive arthritis can arise from exposure to several other foodborne pathogens as well as other non-food related causes.

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