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A Bayesian Approach to Quantify the Contribution of Animal-Food Sources to Human Salmonellosis

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Based on the data from the integrated Danish *Salmonella* surveillance in 1999, we developed a mathematical model for quantifying the contribution of each of the major animal-food sources to human salmonellosis. The model was set up to calculate the number of domestic and sporadic cases caused by different *Salmonella* sero and phage types as a function of the prevalence of these *Salmonella* types in the animal-food sources and the amount of food source consumed. A multiparameter prior accounting for the presumed but unknown differences between serotypes and food sources with respect to causing human salmonellosis was also included. The joint posterior distribution was estimated by fitting the model to the reported number of domestic and sporadic cases per *Salmonella* type in a Bayesian framework using Markov Chain Monte Carlo simulation. The number of domestic and sporadic cases was obtained by subtracting the estimated number of travel- and outbreak-associated cases from the total number of reported cases, i.e., the observed data. The most important food sources were found to be table eggs and domestically produced pork comprising 47.1% (95% credibility interval, CI: 43.3–50.8%) and 9% (95% CI: 7.8–10.4%) of the cases, respectively. Taken together, imported foods were estimated to account for 11.8% (95% CI: 5.0–19.0%) of the cases. Other food sources considered had only a minor impact, whereas 25% of the cases could not be associated with any source. This approach of quantifying the contribution of the various sources to human salmonellosis has proved to be a valuable tool in risk management in Denmark and provides an example of how to integrate quantitative risk assessment and zoonotic disease surveillance.

KEY WORDS: Bayesian inference; Markov Chain Monte Carlo; quantitative risk assessment; salmonellosis; surveillance

1. INTRODUCTION

Salmonellosis is a major cause of foodborne human gastroenteritis in Denmark. Through the last two decades, the annual incidence has primarily shown an increasing trend, but there have been some fluctuations over the years.[1] These fluctuations in incidence were often accompanied by changes in the distribution of *Salmonella* sero and phage types in humans, suggesting that the sources of human salmonellosis changed over time.

In order to get a better understanding of the mechanisms behind the dynamics in the occurrence of *Salmonella* infections in humans, the Danish Zoonosis Centre has previously described a method that estimates the number of human cases attributable to each of the major animal-food sources.[2,3] The principle is to compare *Salmonella* types isolated from animals and foods with *Salmonella* types isolated from humans. In brief, types of *Salmonella* that are exclusively (or almost exclusively) found in a particular food-animal reservoir or food type (unique types) are

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used as "anchor points" for the distribution of types occurring in several reservoirs/sources. It is assumed that all human infections caused by the unique types are associated with the indicated food type or derived from the indicated food-animal reservoir (e.g., pork, beef, slaughter chicken, or eggs). *Salmonella* types that are occurring in several reservoirs are distributed relative to the prevalence of unique types in a given reservoir/food type. Detailed knowledge on the distribution of *Salmonella* types in all relevant food animals and food types, generated through intensive and continuous monitoring, is an essential prerequisite for the analysis. This method, however, takes a deterministic approach and does not include uncertainty of the estimated parameters.

In this article, we present a stochastic model based on the principles of the previous method, but where it is also possible to consider the uncertainty of the estimated parameters. It also enables a more detailed analysis of the differences between the various *Salmonella* serotypes and food materials with regard to their abilities to cause *Salmonella* infections in humans. The model quantifies the individual contribution of the major food sources to cases of human salmonellosis. The results may support risk managers in the assessment of the need for and/or effect of control programs, especially if the model is applied to several years of data. The *Salmonella* statistics from Denmark in 1999 will be used for demonstration.

1.1. Surveillance of Animals, Food, and Humans in Denmark

In Denmark, all major food animals and food of animal origin are monitored for *Salmonella.* The surveillance programs are regularly revised and their contents are described in detail in the annual report of the Danish Zoonosis Centre.[1] In 1999, every commercial flock of layers was regularly (approximately every ninth week) tested for *Salmonella* by a combination of serological and bacteriological methods. All flocks of broilers, turkeys, and ducks were tested by bacteriological examination approximately three weeks prior to slaughter. Every slaughter-pig herd producing more than 100 finishers per year was continuously tested by serology, and herds exceeding a predetermined proportion of seroreactors were followed up by bacteriologic examination. Cattle herds were tested only when there was suspicion of infection. All slaughterhouses took part in the *Salmonella* monitoring in 1999. Every flock of broilers and turkeys was tested after slaughter, and approximately 16,000 end-product samples of pork and 2,000 end-product samples of beef were examined. The number of pork and beef samples collected from each slaughterhouse was proportional to the number of animals slaughtered. Imported products of poultry, pork, and beef were also monitored in 1999. The samples were collected at the importer's premises and the number of samples depended on the amount of imported meat but amounted to approximately 5,000 samples. Altogether more than two million samples from living animals and food of animal origin were tested for *Salmonella* in Denmark in 1999. All isolates of *Salmonella* were submitted to the Danish Institute of Food and Veterinary Research for serotyping, and all isolates of *S.* Typhimurium and *S.* Enteritidis were phage typed.

Cases of human salmonellosis, as well as isolates identified by 10 regional microbiology laboratories, are reported to the Statens Serum Institut (SSI), which is the reference laboratory for enteric pathogens and in charge of the laboratory surveillance system. In 1999, all isolates were serotyped, and all isolates of *S.* Typhimurium and approximately 25% of *S.* Enteritidis isolates were phage typed. Information regarding traveling abroad before disease onset was available for patients, whose stool samples were forwarded to the SSI for analysis. Outbreaks of human salmonellosis may be recognized in the laboratory-based surveillance system, by physicians in general practice and hospitals, and/or by the Regional Veterinary and Food Authority. Recognized outbreaks were reported centrally.[1]

All monitoring data were collated and analyzed at the Danish Zoonosis Centre, a network including the Danish Institute of Food and Veterinary Research, the SSI, and a number of other national institutions involved in monitoring and control of *Salmonella* in Denmark.

2. MATERIALS AND METHODS

2.1. Modeling Techniques—Bayesian Inference Using Markov Chain Monte Carlo

One way of introducing uncertainty in the parameter estimation process for quantitative risk models is to apply the Bayesian inference. The Bayesian approach is based on Bayes's theorem and generally consists of three steps:[4] (1) determining a confidence distribution for the prior estimate of the unknown parameter, (2) finding an appropriate likelihood function, which calculates the probability of observing the actual data for a given value of the unknown parameter, and (3) determining the revised

confidence distribution by multiplying the prior distribution density and the likelihood function. The resulting product is normalized to get the posterior distribution, which describes the knowledge of the parameter after the data have been observed and given the prior belief of the parameter. Normalization of the confidence distribution has, however, been the source of most practical difficulties in Bayesian inference, especially in multidimensional problems, e.g., involving several parameters and where the uncertainty distributions for these are correlated. However, by use of computer-intensive methods it is possible to approximate the theoretical posterior distribution by random draws using Markov Chain Monte Carlo (MCMC) simulation.[4]

Since our model required the evaluation of a multidimensional posterior distribution, we applied MCMC simulation, specifically the Gibbs sampler, to arrive at the posterior distribution. Five independent Markov chains of 30,000 iterations each were run. For each chain, a different set of starting values for the prior distributions were chosen. The starting values were chosen so that they were widely dispersed in the target distributions, since overdispersed starting values can make lack of convergence apparent and ensure that all major regions of the target distributions are represented in the simulations.[4] Five chains were evaluated to be a sufficient number for this purpose. Convergence was monitored using the method described by Gelman and Rubin[4,5] and modified by Brooks and Gelman.[6] In short, convergence was considered to have occurred when the variance between the different chains was no larger than the variance within each individual chain, and when the chains had reach a stable level. The model was set up in the WinBUGS[3] software.[7]

2.2. Structure of the Model

The overall objective of the model was to estimate the number of domestic cases of human salmonellosis that occur sporadically and are attributable to the various animal-food sources.

Salmonella, generally speaking, may cause "sporadic cases" or outbreaks. It is assumed that patients who have not been associated with known outbreaks are sporadic cases. However, this may not always be the case. For example, an increase in the number of isolates of a common pathogen may not be detected because of its high background incidence, or it may be difficult to recognize that the persons who fell ill share a common food source.[8] In this context, a sporadic case is defined as a subject that could not be associated with a recognized outbreak. We are aware that some of these subjects may have been part of the outbreaks that were not recognized in the centralized system, but we believe that most of these outbreaks are small household outbreaks that will have only a minor impact on the model results. However, if such unrecognized outbreaks involve many cases, they can seriously bias the model. The reason is that unrecognized outbreaks caused by *Salmonella* types occurring in only a single animal-food source will tend to overestimate the total number of infections originating from the source harboring this type. In contrast, unrecognized outbreaks caused by *Salmonella* types occurring in several sources will tend to underestimate the total number of infections from the reservoir in question.

A domestic case is defined as a subject who reportedly had not been traveling in approximately one month before disease onset. It is assumed that all cases with a history of traveling were infected abroad.

For ease of explanation, the model description is split into three sections. Section 2.2.1 gives a detailed description of human data input and how the uncertainty about these data was modeled. Section 2.2.2 defines the prior distribution that was used to estimate the expected number of sporadic and domestic cases per *Salmonella* type and food source. Finally, Section 2.2.3 explains how the observed data (i.e., reported number of cases) were combined with the prior distribution in order to estimate the posterior distribution.

2.2.1. Description of Uncertainty about the Human Data

The inputs to the model contain all available information on the number of reported cases per *Salmonella* type, including the number of subjects who reported having traveled abroad or were recognized as being part of an outbreak (Table I). Probability distributions associated with two fundamental stochastic processes, the binomial and the Poisson process, were used to model uncertainty about and variability of the included parameters.[9] The model structure and the parameters used for estimating the "true" number of sporadic and domestic cases of *S.* Typhimurium and *S.* Enteritidis are defined in Table II. The model structure for the remaining serotypes was reduced to uncertainty about the number of travel-related cases, as these serotypes were not phage typed and were not recognized as the cause of any outbreaks.

[3] The WinBUGS code of the model is available from the authors by request.

Table I. Reported Cases of Human Salmonellosis by Sero and Phage Type Available Information on Subjects Who Were Traveling Abroad or Reportedly Were Part of an Outbreak in Denmark in 1999

Salmonella Type ($i = 1$–24)	Reported Human Cases	Outbreak-Related Cases	Cases with a History of Traveling			
			No	Yes	% Travelers	Unknown
S. Enteritidis	2,025	47	1,038	182	14.9	805
PT6	132	0	123	4	3.1	5
PT8	117	0	107	6	5.3	4
PT4	76	0	35	35	50.0	6
PT34	52	47	47	4	7.8	1
PT1	16	0	8	8	50.0	0
Others	61	0	43	17	28.3	1
Not phage typed	1,571	—	675	108	16.0	788
S. Typhimurium	584	91	416	30	6.7	138
DT104	110	61	95	15	13.6	0
DT12	88	0	86	2	2.3	0
DTU288	40	25	38	2	5.0	0
DT17	21	0	20	1	4.8	0
DT170	21	0	20	1	4.8	0
DT66	19	0	19	0	0.0	0
DT120	18	0	16	1	5.9	1
DT193	13	0	13	0	0.0	0
DT110	10	0	10	0	0.0	0
DT135	8	0	8	0	0.0	0
Others	89	5	81	8	9.0	0
Not phage typed	147	—	10	0	0.0	137
S. Hadar	74	0	62	10	13.9	2
S. Agona	60	0	53	5	8.6	2
S. Virchow	59	0	32	26	44.8	1
S. Newport	49	0	38	9	19.1	2
S. Infantis	30	0	27	3	10.0	0
S. Dublin	21	0	18	0	0.0	3
Others incl. NT	366	0	292	62	17.5	12
Total number of cases	3,268	138	1,976	327	14.2	962

Source: Statens Serum Institut.

2.2.1.1. Sero- and Phage-Type Distribution for Reported Cases. A total of 3,268 cases of human salmonellosis were reported in Denmark in 1999. The most frequently occurring serotypes were *S.* Enteritidis (2,025 cases) and *S.* Typhimurium (584 cases). *S.* Hadar, *S.* Agona, *S.* Virchow, *S.* Newport, *S.* Infantis, and *S.* Dublin, comprised approximately 44% of the other 659 cases and were included separately in the model (Table I). The remaining serotypes were grouped into "other serotypes" because a major part of these had caused only a few infections each, and many of these serotypes were not observed in the animal reservoirs.

Phage typing results were available for 454 (22%) of the *S.* Enteritidis cases and 437 (75%) of the *S.* Typhimurium cases. Five phage types of *S.* Enteritidis and 10 phage types of *S.* Typhimurium were included separately in the model, whereas phage types causing only a few infections were grouped into "other phage types" (Table I). Generally, these phage types also occurred infrequently in the animal reservoirs.

For 1,571 cases of *S.* Enteritidis and 147 cases of *S.* Typhimurium the phage type was unknown. The proportions used to allocate cases with an unknown phage type within each of these serotypes were estimated based on the observed distribution of the cases that had been phage typed assuming similar phage-type distribution of cases with and without a phage type (u_i in Table II). However, for 108 subjects with unknown phage type that answered yes to having traveled, a phage type was allocated by using the phage-type distribution for travelers only and assuming that this distribution was equal for travelers with known and unknown phage type. This approach was chosen because the phage-type distribution of known travelers differed from the phage-type distribution of known domestic cases, and it would consequently be incorrect to use the overall phage-type distribution

Table II. Description and Definition of Parameters Used to Estimate the Number of Sporadic and Domestic Cases per *Salmonella* Types[a]

Notation	Description	Estimation
i	Subscript for *Salmonella* type (sero and phage type)	—
o_i	Observed cases affected with phage i	Data
ob_i	Observed cases affected by phage i and known to be outbreak related. For each outbreak one case was subtracted so that one outbreak contributed with one sporadic case	Data
yt_i	Observed cases affected by phage i answering yes to have traveled	Data
nt_i	Observed cases affected by phage i answering no to have traveled	Data
pt_i	Observed cases affected by phage i, but with unknown travel history	Data
NPT	Total number of cases not phage typed	Data
YTNP	Total number of cases not phage typed, but answering yes to have traveled	Data
UTNP	Total number not phage typed and with unknown travel history	Data
α_i	Probability that a person of phage i with unknown travel history did travel. The beta distribution reflects the uncertainty about the true proportion of travelers	$\text{Beta}(yt_i + 1; nt_i + 1)$
dt_i	Estimated additional number of people with phage i that had been traveling. The binomial distribution reflects the variability about the true proportion of travelers	$\text{Bin}(pt_i; \alpha_i)$
pyt_i	Probability that a case with unknown phage type and answering yes to have traveled belongs to phage i	$\text{Dirichlet}(yt_i + 1)$
$ytnp_i$	Estimated number of cases without phage type but answering yes to have traveled who were affected with phage i and did travel	$pyt_i \times \text{YTNP}$
u_i	Proportion to allocate cases with unknown phage type. The gamma distribution reflects the uncertainty of o_i	$\text{Gamma}(o_i; 1)$ $\Sigma\text{Gamma}(o_i; 1)$
et_i	Estimated number of people without phage type and travel history who were affected with phage i and did travel	$\text{Bin}(u_i \times \text{UTNP}; \alpha_i)$
Travel	Estimated total number of travel-related cases	$\Sigma yt_i + \Sigma dt_i + \Sigma ytnp_i + \Sigma et_i$
pob_i	Probability that a case with phage type i was outbreak related	$\text{Beta}(ob_i + 1; o_i - ob_i + 1)$
eob_i	Estimated additional number cases without phage type that belonged to an outbreak caused by phage type i	$\text{Bin}(u_i \times \text{NPT}; pob_i)$
Outbreak	Estimated total number of outbreak-related cases	$\Sigma ob_i + \Sigma eob_i$
$spdo_i$	Estimated number of sporadic and domestic cases of phage type i	$o_i - ob_i - yt_i - dt_i$
$pspdo_i$	Proportion to allocate sporadic and domestic cases of unknown phage type	$\text{Gamma}(spdo_i; 1)$ $\Sigma\text{Gamma}(spdo_i; 1)$
espdo_i	Estimated number of sporadic and domestic cases without phage type belonging to phage type i	$(\text{NPT} - \text{YTNP} - \Sigma et_i - \Sigma eob_i) \times pspdo_i$
x_i	Estimated number of sporadic and domestic cases infected by phage type i	$spdo_i + espdo_i$

[a]The model structure shown is for *S.* Enteritidis and *S.* Typhimurium. The structure for the remaining serotypes was reduced to uncertainty about the number of travel-related cases, as these serotypes were not phage typed and not recognized as the cause of any outbreaks.

for allocating phage types for known travelers. The phage-type proportions for the 108 known travelers were modeled by use of the Dirichlet distribution (pyt_i in Table II). The Dirichlet distribution is the conjugate to the multinomial distribution, much like the beta distribution is the conjugate to the binomial distribution. The parameters of the Dirichlet distribution is $(\alpha_1, \alpha_2, \ldots, \alpha_n) = (yt_1 + 1, yt_2 + 1, \ldots, yt_n + 1)$, where yt_i is the number of travel-related cases of phage type i. So for each phage type, the Dirichlet distribution estimates a probability that a randomly chosen travel-related case with unknown phage type will belong to this phage type and, obviously, all these probabilities have to add up to 1.

2.2.1.2. The Number of Outbreak-Related Cases. In 1999, six different outbreaks involving a total of 138 cases were reported (Table I). Three outbreaks were caused by multidrug resistant *S.* Typhimurium DT104 and comprised a total of 61 culture-confirmed cases. Also, an increase in the number of *S.* Typhimurium DTU288 was noted in the beginning of 1999, where 25 reported cases primarily from the same geographic area suggested the occurrence of a common source outbreak. Another outbreak by an unusual *S. typhimurium* phage type (grouped into "other phage types" in Table I) occurred in a nursing home and involved five patients. Finally, a general outbreak of *S.* Enteritidis PT34 had an impact on the overall *S.* Enteritidis phage-type distribution. The outbreak occurred over a six-week period, and at least 47 culture-confirmed cases were reported.[1] Before including these numbers of outbreak-related cases in the model, one case per outbreak was extracted and added to the sporadic cases so that each outbreak

contributed one sporadic case. Based on this, a total of 132 (138 − 6) cases were included as input for modeling the number of outbreak-related cases. However, since only approximately 22% of human *S.* Enteritidis and 75% of the *S.* Typhimurium isolates were phage typed, the true number was probably somewhat higher. We adjusted for this uncertainty using the binomial distribution to estimate the additional number of outbreak-related cases per phage type (eob_i) by assuming that the probability of cases relating to an outbreak (pob_i) caused by a specific phage type was similar for cases with and without a phage type (Table II).

2.2.1.3. The Number of Travel-Associated Cases. Table I shows available travel information. The proportion of travelers with *S.* Enteritidis infections varied widely between phage types. Around 50% of cases with PT4 and PT1 had been traveling, compared with less than 10% of other commonly encountered phage types. Of all cases of *S.* Enteritidis with a known travel history, 182 (14.9%) had been abroad before falling ill (Table I). For cases of *S.* Typhimurium, 30 (6.7%) cases in total had been traveling outside Denmark before disease onset. The proportion of travelers was highest among cases infected with *S.* Typhimurium DT104 (13.6%), which also was the most frequently occurring phage type (Table I). There was some variation in the proportion of travel-associated cases among the remaining serotypes, ranging from 44.8% for cases of *S.* Virchow to 0% for cases of *S.* Dublin. Overall, 327 (14.2%) of 1,976 cases had been abroad before disease onset. For 962 cases, no travel information was available (Table I). Assuming that the probability (α_i) of travelers with a particular *Salmonella* type was equal for known and unknown travelers, the traveling status of these cases was estimated by use of the binomial distribution (Table II).

2.2.1.4. The Estimated Number of Sporadic and Domestic Cases per Salmonella Type. The number of sporadic and domestic cases was estimated for each *Salmonella* type by taking the reported number of cases, adding the additional number of cases estimated from those with unknown phage type, and then subtracting the estimated number of travel- and outbreak-related cases as shown in Table II.

2.2.2. The Prior Distribution

The prevalence of *Salmonella* in the major reservoirs and the distribution of the different *Salmonella* sero- and phage types in animals, food, and humans constitute the key data for quantifying the sources of human salmonellosis. The principle behind the model is to compare the number of human cases caused by different *Salmonella* types with the prevalence of the *Salmonella* types isolated from the different food sources, weighted by the amount of food source consumed. It is a prerequisite for the application of this type of analysis that some of the frequently occurring *Salmonella* types are heterogeneously distributed between the different animal and food sources. The number of infections caused by *Salmonella* types that occur more homogeneously may then be estimated based on the prevalence of the heterogeneously distributed types.

However, the number of people being infected by a particular *Salmonella* type occurring in a particular source may also depend on additional factors than the prevalence and amount of food source consumed. These factors include:

1. Bacteria-dependent factors due to differences between *Salmonella* types in, for example, survivability during the food processing and/or in ability to cause disease in humans (virulence/pathogenicity).
2. Food-source-dependent factors due to differences between food types in characteristics that affect their ability to act as vehicles for foodborne infections (e.g., general differences in bacterial load, food characteristics influencing growth behavior, or preparation procedures), or affect the prevalence estimates, i.e., differences in monitoring systems and analyzing methods.

The equation used to estimate the expected (i.e., Poisson intensity) number of human cases per source and *Salmonella* type was defined as follows (see Table III):

$$\lambda_{ij} = M_j p_{ij} q_i a_j,$$

where λ_{ij} is the expected number of cases/year of type i from source j; M_j, the amount of source j available for consumption/year (Table IV); p_{ij}, the prevalence of type i in source j (Table IV); and q_i, the bacteria-dependent factor for type i; and a_j, the food-source-dependent factor for source j.

It was assumed that the $\{q_i\}$ for phage types within *S.* Enteritidis and *S.* Typhimurium were equal. Furthermore, because the values of $\{q_i\}$ are all relative, we fixed q for *S.* Enteritidis phage types at 1, which reduced the number of estimated parameters by 1 and made the comparisons easier.

Table III. Description and Definition of Parameters Used to Estimate the Number of Sporadic and Domestic Cases per Animal-Food Source

Notation	Description	Estimation
i	Subscript for *Salmonella* type (sero and phage type)	—
j	Subscript for food source	—
M_j	Amount of food source available on the Danish market in 1999 in million kg or million eggs	Data
p_{ij}	Prevalence of *Salmonella* type i in food source j	Data
q_i	Bacteria-related factors. We operated with a factor for each *Salmonella* serotype with the one for *S.* Enteritidis fixed at 1. Phage types within *S. enteridis* and *S.* Typhimurium were assumed to have equal qs	q_1–$q_6 = 1$ $q_7 = \text{Uniform}(0; 10)$ q_8–$q_{17} = q_7$ q_{18}–$q_{24} = \text{Uniform}(0; 10)$
a_j	Food-source-related factors. It was assumed that this factor was equal for Danish and imported pork, and Danish and imported beef. In total, 7 a_js (pork, beef, eggs, broilers, turkeys, ducks, and imported poultry) were included in the model	a_1–$a_6 = \text{Uniform}(0; 0.01)$ $a_7 = a_1$ $a_8 = a_2$ $a_9 = \text{Uniform}(0; 0.01)$
λ_{ij}	Estimated expected number of sporadic and domestic cases infected by *Salmonella* type i in food source j	$M_j \times p_{ij} \times q_i \times a_j$
λ_i	Estimated expected number of sporadic and domestic cases infected by *Salmonella* type i. Corresponds to x_i in Table II	$\sum_j \lambda_{ij}$
λexp_i	Expected number of observed cases affected with type I	$\lambda_i + ob_i + yt_i + dt_i - \text{espdo}_i$
o_i	Observed people affected with type i. Assumed to be Poisson distributed with $\lambda_i = \lambda\text{exp}_i$	$\text{Poisson}(\lambda exp_i)$
Unknown	Estimated total number of sporadic and domestic cases belonging to the group of "other serotypes" or "other phage types" and therefore not attributed to any animal-food sources	$\sum_j (\lambda_{6,j} + \lambda_{17,j} + \lambda_{24,j})$
λ_j	Estimated total number of sporadic and domestic cases infected from food source j	$\sum_i \lambda_{ij}$

The above equation represents the multiparameter prior, where $\{q_i\}$ and $\{a_j\}$ were parameters of unknown value. They were included in the model as uniform distributions, as defined in Table III. For all the uniform distributions, the lower limits were set to 0. In order to check that we had set the upper limits for $\{q_i\}$ and $\{a_j\}$ sufficiently wide to encompass any reasonable values for the parameters, plots of the posterior density functions were visually examined. If any of these plots indicated that the distributions were arbitrarily cut off at the upper value, the uniform distributions were redefined and the model was rerun. When the prior minima and maxima efficiently spanned the required ranges, the final model was run.

The bacteriological surveillance data that were used for inputs to the model are presented in Table IV. The prevalence of the different *Salmonella* types in pork, beef, and imported meat were calculated as the percentage of positive samples. In slaughter-poultry flocks, data were obtained from the ante mortem examination performed at flock level approximately three weeks before slaughter. The prevalence is therefore expressed as the percentage of positive flocks. It is therefore assumed that infected flocks of the same species are contributing equally to the number of human cases. Or, in other words, it is assumed that both the within-flock prevalence and the number of birds in flocks of the same species are the same. In table-egg layers, where the flock size varied from a few birds, e.g., in flocks producing eggs for barnyard sale, to more than a 100,000 in flocks producing eggs for authorized egg-packing centers, we adjusted the prevalence estimates according to flock size (data on flock sizes not shown). It is consequently assumed that the number of contaminated table eggs produced by an infected flock is proportional to the flock size, so that infected flocks of the same size contribute equally to the number of human cases. For this reason, the proportion of positive flocks ($35/718 = 4.9\%$) is not equal to the total prevalence (10.4%) given in Table IV. We also included information on the amount (in million kg) of different meat types and shell eggs available for consumption at the Danish market in 1999 as reported in the national statistics.[10–12]

2.2.3. The Posterior Distribution

The model was set to calculate the expected number of cases per *Salmonella* type (λ_i) according to the above equation. From this λ_i, we made a

Table IV. Prevalence (in%) of *Salmonella* Sero- and Phage Types in Meat and Poultry Flocks, and the Amount of the Food Stuffs Available for Consumption in Denmark in 1999

	Animal-Food Source ($j = 1$–9)								
Salmonella type ($i = 1$–24)	Cuts of Pork	Cuts of Beef	Layer Animals	Broiler Flocks	Turkey Flocks	Duck Flocks	Imported Meat		
							Pork	Beef	Poultry
S. Enteritidis	0.006	0.051	9.703	0.127	0	2.899	0.739	0	1.276
PT6	0	0	4.236	0.064	—	0	0	—	0.232
PT8	0	0	3.683	0.042	—	0	0	—	0.077
PT4	0	0	0.642	0.021	—	0	0.148	—	0.928
PT34	0	0	0.286	0	—	0	0	—	0
PT1	0	0	0	0	—	0	0.443	—	0
Others including NT[a]	0.006	0.051	0.856	0	—	2.899	0.148	—	0.039
S. Typhimurium	1.110	0.101	0.539	1.294	0	0.483	3.250	0.181	1.663
DT104	0.006	0	0	0	—	0	1.477	0.121	0.696
DT12	0.457	0	0	0.085	—	0	0	0	0.039
DTU288	0.006	0	0	0	—	0	0	0	0
DT17	0.128	0	0	0	—	0	0.148	0	0
DT170	0.110	0	0	0	—	0	0	0	0
DT66	0.140	0	0	0.106	—	0	0	0	0
DT120	0.006	0	0	0	—	0	0	0.060	0.232
DT193	0.061	0	0	0	—	0	0.148	0	0.039
DT110	0.012	0	0.539	0.254	—	0	0	0	0
DT135	0	0	0	0.170	—	0	0	0	0
Others including NT[a]	0.183	0.101	0	0.679	—	0.483	1.477	0	0.657
S. Hadar	0	0	0	0.042	0	23.671	0	0	4.099
S. Agona	0.006	0	0	0.042	0.820	0	0	0	0.503
S. Virchow	0	0	0	0.021	0	0	0	0	1.392
S. Newport	0	0	0	0	2.186	0	0	0	1.856
S. Infantis	0.165	0	0.196	0.615	0	0	0.295	0	1.276
S. Dublin	0.006	0.558	0	0	0	0	0	0.302	0
Others including NT[a]	0.628	0.304	0	1.527	3.279	65.700	3.693	0	12.490
Total prevalence	1.921	1.015	10.438[b]	3.668	6.284	92.754	7.977	0.484	24.555
No. of positive samples/flocks	315	20	35	173	23	192	54	8	635
No. of samples	16,399	1,971	718	4,716	366	207	677	1,654	2,586
Amount of food stuff available for consumption (million kg)	251.9	51	66.8	76.1	3	2.6	17.9	83	23.7

Source: Danish Veterinary and Food Administration and Danish Institute of Food and Veterinary Research.
[a]Not typable isolates.
[b]Prevalence weighted by the flock size (data not shown).

back-calculation by adding the number of travel- and outbreak-related cases with known phage type (yt_i, dt_i, and ob_i) and subtracting the number of sporadic cases without phage type ($espdo_i$) in order to get the expected number of reported cases ($\lambda\exp_i$). The observed data (o_i) were then linked with the prior distribution ($\lambda\exp_i$) by assuming that the observed number of cases per *Salmonella* type (o_i) were Poisson distributed with a parameter value equal to the expected number of cases ($\lambda\exp_i$). In other words, the model was set to estimate the multidimensional posterior distribution for $\{a_j\}$ and $\{q_i\}$ assuming that $o_i \sim$ Poisson($\lambda\exp_i$). A Poisson process is reasonably justifiable as a low-probability approximation to a binomial process, where an item of food is a trial and its probability of causing illness is very low. A Poisson process is further justified if one considers the volume of food consumed to be a continuous exposure of humans to a medium containing food pathogens, rather than a discrete exposure of humans to food items containing pathogens.

3. RESULTS

The model estimated that the total expected number of reported *Salmonella* cases in Denmark in 1999 was 3,285 (95% Bayesian, CI: 2,754–3,876), which is in good agreement with the observed number of 3,268. Of the 3,285 expected cases, 490 were estimated to be

Table V. Estimated Major Sources of Cases of Human Salmonellosis in Denmark in 1999

	Estimated Number of Cases					Percentage of Domestic and Sporadic Cases			Percentage of All Cases		
Source	Mean	*SD*	Median	95%	CI[a]	Mean	95%	CI[a]	Mean	95%	CI[a]
Pork	221	15.9	220	192	254	9.0	7.8	10.4	6.7	5.8	7.7
Beef	12	2.5	11	7	17	0.5	0.3	0.7	0.4	0.2	0.5
Eggs	1,156	47.1	1,156	1,063	1,247	47.1	43.3	50.8	35.2	32.4	38.0
Broilers	87	27.1	82	45	151	3.5	1.8	6.1	2.6	1.4	4.6
Turkeys	44	26.1	43	2	94	1.8	0.1	3.8	1.3	0.1	2.9
Ducks	28	16.3	27	2	61	1.1	0.1	2.5	0.8	0.1	1.9
Imported pork	90	11.3	90	70	114	3.7	2.9	4.7	2.7	2.1	3.5
Imported beef	56	9.4	56	38	75	2.3	1.6	3.1	1.7	1.2	2.3
Imported poultry	144	70.3	147	15	276	5.9	0.6	11.2	4.4	0.5	8.4
Travel related	490	17.8	490	457	526	—	—	—	14.9	13.9	16.0
Outbreak related	341	24.6	340	296	392	—	—	—	10.4	9.0	11.9
Unknown source	616	26.4	615	566	669	25.1	23.1	27.3	18.8	17.2	20.4
Total	3,285					100			100		
Sporadic	2,453					100			74.7		
Attributable to source	2,669					74.9			81.2		

[a]Bayesian credibility interval.

associated with traveling abroad and 341 to be outbreak related, leaving 2,453 (95% CI: 2,001–2,958) cases that were acquired in Denmark and occurred sporadically (Table V). The observed (o_i) and expected number ($\lambda \exp_i$) of cases per *Salmonella* type is plotted in Fig. 1.

The result of quantifying the contribution of animal-food sources to human salmonellosis is presented in Table V. The major source of infection was table eggs, to which 47% (95% CI: 43.3–50.8%) of the domestic and sporadic cases could be attributed. This was followed by domestically produced pork and imported poultry, which comprised 9% (95% CI: 7.8–10.4%) and 6% (95% CI: 0.6–11.2%) of the cases, respectively. However, the credibility limits for imported poultry were wide. Taken together, the imported foods (pork, beef, and poultry) were estimated to account for approximately 12% of the domestic

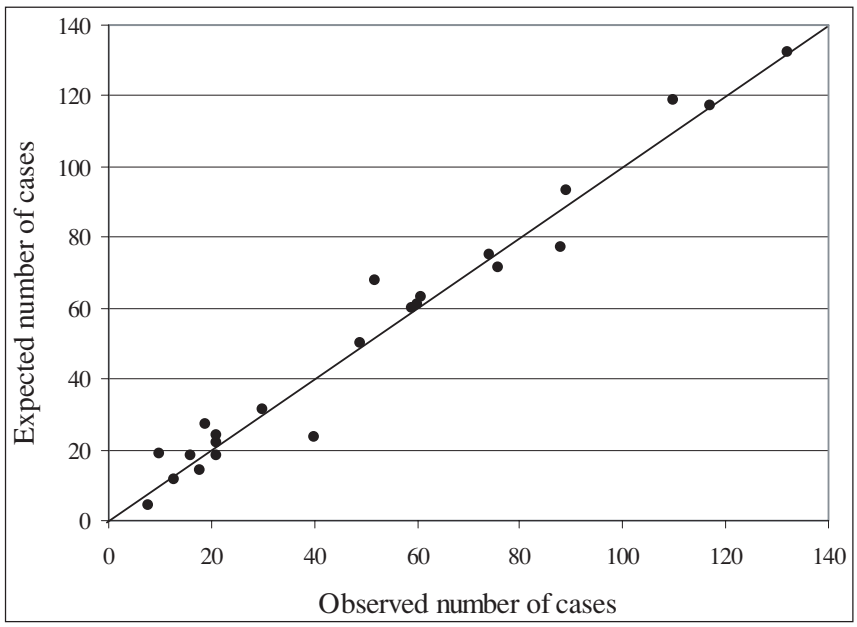

Fig. 1. Plot of the observed and expected values of the number of reported cases per *Salmonella* type.

Table VI. Estimated Values of the Food-Source and Bacteria-Dependent Factors: $\{a_j\}$[a] and $\{q_i\}$

	Mean	Rank	*SD*	Median	95%	CI[b]
a[pork and imported pork]	0.58	3	0.10	0.58	0.40	0.80
a[beef and imported beef]	2.09	2	0.53	2.07	1.12	3.21
a[eggs]	0.19	6	0.01	0.19	0.18	0.21
a[broilers]	0.34	4	0.10	0.32	0.17	0.57
a[turkeys]	3.11	1	11.23	0.86	0.02	18.66
a[ducks]	0.21	5	0.21	0.15	0.00	0.75
a[imported poultry]	0.15	7	0.12	0.14	0.00	0.41
q[*S.* Enteritidis]	1	3	—		—	—
q[*S.* Typhimurium]	0.15	6	0.03	0.15	0.11	0.21
q[*S.* Hadar]	0.44	5	0.57	0.25	0.08	2.16
q[*S.* Agona]	1.04	2	0.72	0.88	0.11	2.81
q[*S.* Virchow]	1.29	1	1.49	0.65	0.20	5.77
q[*S.* Newport]	0.75	4	1.32	0.30	0.03	5.11
q[*S.* Infantis]	0.06	7	0.02	0.06	0.03	0.09
q[*S.* Dublin]	0.02	8	0.01	0.02	0.01	0.04

[a]Values of the $\{a\}$s are in 10^{-5}.
[b]Bayesian credibility interval.

and sporadic cases, whereas the remaining Danish-produced foods (broilers, turkey meat, duck meat, and beef) comprised around 7% of the cases (Table V). Approximately 25% of the cases could not be associated with any of the sources. As per definition, all domestic and sporadic cases allocated to either the group of "other serotypes" or to *S.* Typhimurium and *S.* Enteritidis, "other phage types," were classified as unknown, because the grouping made it impossible for the model to distribute cases according to the prevalence of the different *Salmonella* types in the food sources. The proportion of cases with unknown origin may, therefore, be reduced if more sero- and phage types are included individually in the model.

The highest value for the food-source dependent factors $\{a_j\}$ was found for turkey meat followed by those for beef and pork, whereas the lowest was found for imported poultry. However, the confidence range for turkey meat was very wide (Table VI). Therefore, disregarding turkey meat, the results suggest that a kilogram of salmonella-contaminated beef has a higher probability of causing an infection than a kilogram of any of the other food.

The estimated values for the bacteria-dependent factors are also presented in Table VI. The results suggest that the ability of *S.* Enteritidis (q[*S.* Enteritidis] was fixed at 1) to survive food processing and/or cause disease is almost seven times greater than that of *S.* Typhimurium ($q = 0.15$, 95% CI: 0.11–0.21), and 17 and 50 times greater than that of *S.* Infantis and *S.* Dublin, respectively. For the remaining serotypes (*S.* Virchow, *S.* Agona, *S.* Newport, and *S.* Hadar), the distributions were skewed with a long left tail and the credibility limits were wide, making ranking more difficult to interpret (Fig. 2). However, the mean values suggest that they all are ranking above *S.* Typhimurium with the $\{q\}$s for *S.* Agona and *S.* Virchow being close to that for *S.* Enteritidis (Table VI).

4. DISCUSSION

Despite many efforts to prevent and control foodborne salmonellosis during the last two decades, *Salmonella* continues to be one of the leading causes of human gastroenteritis in most countries around the world.[13,14] In recent years, several countries have implemented national *Salmonella* surveillance and control programs to improve food safety for meat and poultry products.[13,15–19] Furthermore, the coming revision of the EU "Zoonosis directive" (92/117/EEC) is expected to be extended to include surveillance and control of *Salmonella* in other species than poultry breeders.

To date, risk assessment in relation to foodborne salmonellosis has primarily used a semi-quantitative approach based on outbreak data, case-control studies, and expert opinion. So, even though many articles have been published on the detection and control of *Salmonella* in animals and food, there exist only limited data that provide evidence for the success (or failure) of national and international control programs in terms of reducing human salmonellosis.[20] Being able to quantify the contribution of the various food sources is an important tool in risk management.

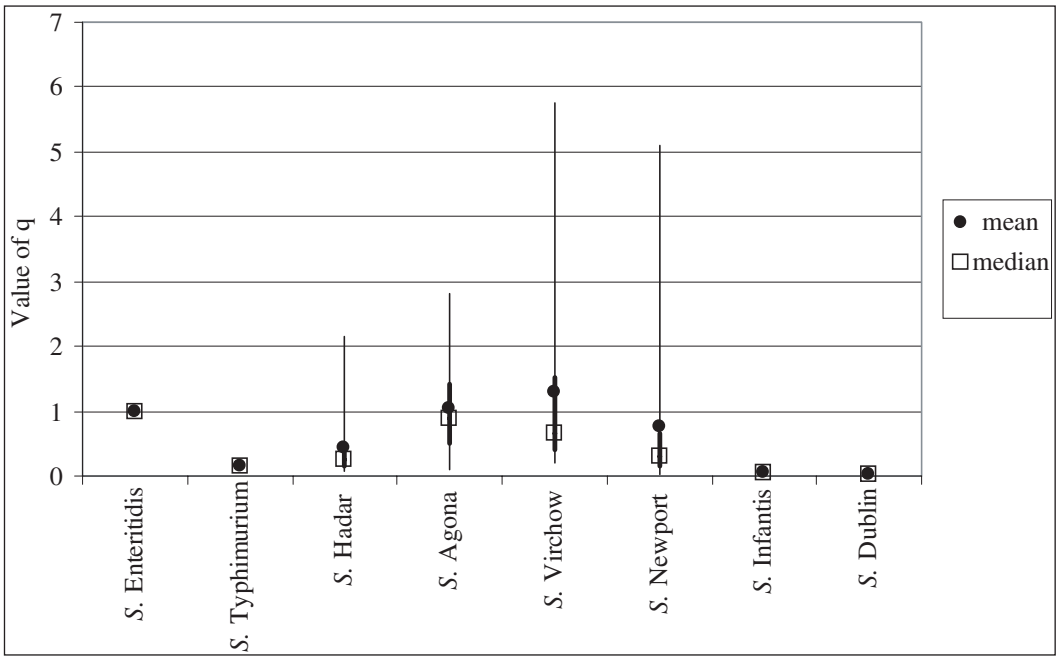

Fig. 2. Mean and median values of the serotype-dependent factors $\{q\}$. The bold error bars illustrate the range of the 50% credibility interval, i.e., the 25–75% percentiles. The light error bars illustrate the range of the 95% credibility interval, i.e., the 2.5–97.5% percentiles.

In addition to evaluating the trends and dynamics of sources to human salmonellosis, quantitative analyses support risk managers in their decision of allocating resources in order to achieve the highest possible public health benefit. Since the early 1990s, the control of *Salmonella* in Denmark has been based on such an integrated quantitative risk-based approach that is able to document the needs for, as well as the effects of, the program.[1]

The method requires intensive monitoring of all relevant food animals, foods, and humans, providing estimates of the *Salmonella* prevalence in the different sources followed by the application of discriminatory epidemiological typing methods, notably sero and phage typing. It is not sufficient only to have information of the serotype distributions. This might explain why some studies comparing isolates from animals and humans conclude that raw animal products may not be among the primary sources of human salmonellosis.[21] The requirement of intensive monitoring makes the model less applicable in some countries. However, the general concept is applicable even with less robust data. For instance, many countries may have estimates of the overall *Salmonella* prevalence in the various food sources obtained from, e.g., surveys as well as information of the sero- and phage-type distributions obtained either from the same surveys or from laboratory databases. The overall prevalence estimates can be included directly in the model as informed prior distributions, which are subsequently linked with the relevant sero- and phage-type distribution in order to obtain prior estimates of the subtypes-specific prevalences. This approach will, obviously, increase the total uncertainty in the model, but this seems quite acceptable since the data quality is reduced.

Contaminated vegetables or fruit, pets, or other sources not routinely monitored in Denmark undoubtedly also cause some cases of human salmonellosis. Some of these are probably attributed to the unknown category, whereas others may incorrectly be attributed to one of the major sources. This may be acceptable if the contamination originated from an animal reservoir, for instance, pets fed contaminated meat or vegetables irrigated with water contaminated with animal manure. Furthermore, most published work suggests that vegetables and fruit often are associated with outbreaks.[22–26] Based on this, we believe that the majority of foodborne incidences related to vegetables and fruit in Denmark will be identified as part of outbreaks, and will be included in the model as such even though the products are

not routinely monitored. Reptiles and turtles kept as pets have been described as primary sources of sporadic human infections caused by infrequently occurring serotypes.[27–29] These infections are presumably attributed to the unknown category. Finally, some cases of *S.* Enteritidis with unknown origin may have been caused by imported eggs, which are currently not monitored in Denmark. However, according to official reports, the vast majority of imported eggs are used for further processing, where they are subjected to heat treatment.

Although the zoonotic *Salmonella* types can occur in almost all food-producing animals, there are often rather strong associations between certain types and a particular animal reservoir.[30,31] This was also the case in Denmark in 1999, where some *Salmonella* types were found only in a single reservoir (Table IV). A heterogeneous distribution of *Salmonella* types is a prerequisite for the model to find the solution with the highest probability of occurrence. There would be little information contained in the observations of human cases for this assessment if the *Salmonella* types were more or less equally distributed among the food sources, and the model would result in a very diffuse posterior distribution. In our model, we saw signs of this, as the distributions of the number of cases attributable to imported poultry and turkeys were rather wide. This may be explained by the fact that the *Salmonella* types predominating in these two sources were found frequently in other sources as well (Table IV). In future models, we will be able to divide the group of imported poultry into broilers, turkeys, and ducks, which is expected to improve the model results.

Uncertainty about the prevalence of *Salmonella* in the different food sources was not included in the model. The reason was that inclusion of uncertainty as beta distributions results in prevalence estimates that are biased toward 50%, i.e., an overestimation, when the apparent prevalence is very low or zero. This is because a beta (α,β) distribution has a mean of $\frac{\alpha}{\alpha+\beta}$ and thus a beta $(s+1, n-s+1)$ distribution has a mean of $\frac{s+1}{n+2}$. No observations of certain strains in some food sources precluded the use of the unbiased beta (s, $n-s$) distribution that would be undefined for $s = 0$. Furthermore, by introducing uncertainty about the food-source prevalences, we would get above-zero prevalence estimates for *Salmonella* types in food sources where, in all probability, they do not occur, which in fact would weaken the above-mentioned heterogeneity prerequisite. Based on this and the relatively intensive *Salmonella* surveillance in Denmark, we assessed that the most valid results were obtained by keeping the food-source prevalences fixed.

Microbial risk assessment has been recognized for some time as an important tool for supporting the management of human health risks posed by foodborne pathogens.[32] Unfortunately, the complexity and dynamic nature of food production as well as the dose-response relationship of foodborne disease make mathematical modeling of the stable-to-table chain difficult and often leads to models based on a large number of assumptions with limited validity. For instance, the commonly applied Gompertz growth model used for microbial predictive modeling is based on the assumption that all types of the pathogen being modeled have equal ability to survive and grow through processing and cooling.[33–35] Similarly, the beta-Poisson model commonly used for dose-response modeling assumes that all types of the pathogen have equal ability to cause infections in humans, i.e., equal virulence or pathogenicity. At least for *Salmonella*, a genus comprising more than 2,300 serotypes, both experimental studies and epidemiological observations contradict this. For instance, in many countries, *S.* Derby is a very common serotype in pigs and pork, but is rarely isolated from humans.[36–39] The same has been observed for *S.* 4.12:b:- in broilers in Denmark.[40] Therefore, in order to avoid making assumptions about equal survivability and/or virulence between serotypes, we included the bacteria-dependent factors $\{q_i\}$ in the model.

Some will probably argue that the $\{q_i\}$ for the phage types should also be allowed to vary. However, as the assessment is based on the comparison of relative numbers, we had to assume similarity between some of the *Salmonella* types. We therefore chose to assume similar survivability/pathogenecity of phage types within the same serotype. The fact that some of the most important virulence factors are related to the serotype (e.g., the length of the LPS O-chain) or the presence of virulence plasmids[41,42] supports this assumption, whereas we did not succeed in finding any references describing phage-type-dependant virulence factors. Against the assumption is the emergence of the multidrug-resistant *Salmonella* strains, where the resistance apparently is associated with particular phage types, e.g., *S.* Typhimurium DT104. There are indications that these strains increase the risk of infection as well as cause more severe infections than nonresistant strains.[43–45] In future models, we will explore the possibility of including information of resistance patterns, i.e., adjusting the model to

include a separate $\{q_i\}$ for some resistance patterns within specific sero or phage types.

Some of the same considerations as discussed for the bacteria-dependent factors applied when we chose to include the food-source dependent factors $\{a_j\}$. Food types have different characteristics, some of which influence their ability to act as vehicles for foodborne infections.[41] Besides the more physical properties like water activity, pH, etc., these may include general differences in bacterial load, applied processing procedures, or usual preparation methods. For instance, we found the food-source-dependent factor, for beef to be relatively high, which is compatible with the fact that beef compared to most of the other food sources, often is consumed raw or only slightly cooked. Also, in food sources where the prevalence is relatively high, the bacteria concentration (i.e., CFU per gram) may tend to be higher.[46] Such food sources will tend to cause relatively more infections directly, but maybe also indirectly due to a higher probability of cross-contamination of other foods. In the present model, the food-dependent factors also included differences in the applied surveillance method, e.g., sampling material and culturing method.

It is underlined that the estimated values of the bacteria- and food-source-dependent factors are simply multiplication factors that helped us arrive at the most probable solution given the observed data. Their relative size can provide an idea about the differences between *Salmonella* types and food types with respect to causing human infections. However, the estimates were based on the observed data for only a single year, 1999, and should as such be interpreted with care. In future studies we will investigate the relative relationship between the estimates when the model is applied to data from several years.

As mentioned in Section 1, we have previously used a deterministic approach to estimate the number of cases attributable to various animal-food sources.[2,3] In Fig. 3, we have made a comparison of the results using both methods based on the data from 1999. The principles and assumptions of the two methods are basically the same, but because the deterministic approach does not include the bacteria- and food-source-dependent factors, some subjective assessment regarding the impact of, e.g., the different food sources, were unavoidable. Compared to the quantitative model, the deterministic approach generally tends to overestimate the impact of the

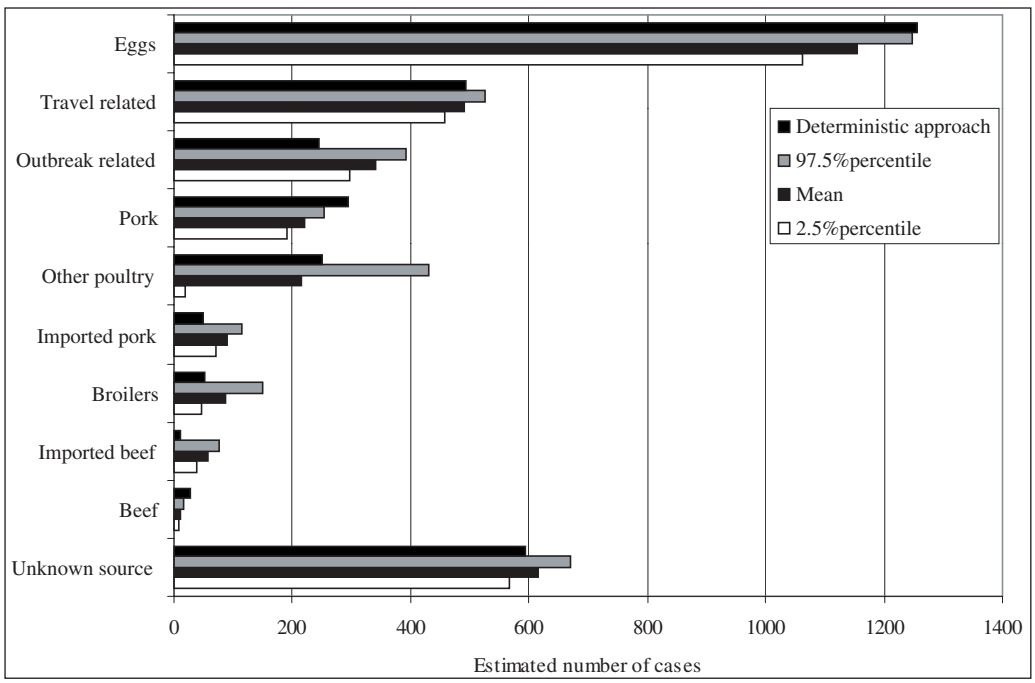

Fig. 3. Comparison of the results obtained by the previously used deterministic approach and the quantitative model (mean, 2.5, and 97.5% percentiles) presented in this article. The group of "other poultry" consists of Danish-produced turkey and duck meat, and imported poultry of various kinds.

Danish-produced foodstuff and underestimate the impact of the imported foodstuff, which is probably explained by the more subjective assessment taken using the deterministic approach. For the 1999 data, we did not attempt to distinguish between Danish-produced turkey meat, duck meat, and imported poultry meat by the deterministic approach, as we evaluated the uncertainty to be too large. Notably, the credibility limits for the number of cases attributable to these sources by the quantitative model were also quite large (Table V). In Fig. 3, turkey meat, duck meat, and imported poultry meat are, therefore, grouped into other poultry.

Like all quantitative risk models, the model presented in this article reflects a simplification of the real world, but by applying the method regularly, for instance, on a yearly basis, as we have done in Denmark, it is possible to monitor the main sources and dynamics in the occurrence of human salmonellosis and to improve the estimation of the model parameters. We use the model regularly to provide estimates of the benefits of certain risk management actions. For example, the change in human salmonellosis incidence associated with a given source if the prevalence of *Salmonella* in that source were reduced by, say, 50%. Used as such, the model provides an extremely powerful tool for risk managers in assessing the need for and/or effect of *Salmonella* control programs.

Finally, we would like to encourage other countries to apply this method on their *Salmonella* surveillance data. This would further promote the integration of quantitative risk assessment and zoonotic disease surveillance.

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