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Uncertainty of Population Risk Estimates for Pathogens Based on QMRA or Epidemiology: A Case Study of *Campylobacter* in the Netherlands

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Epidemiology and quantitative microbiological risk assessment are disciplines in which the same public health measures are estimated, but results differ frequently. If large, these differences can confuse public health policymakers. This article aims to identify uncertainty sources that explain apparent differences in estimates for *Campylobacter* spp. incidence and attribution in the Netherlands, based on four previous studies (two for each discipline). An uncertainty typology was used to identify uncertainty sources and the NUSAP method was applied to characterize the uncertainty and its influence on estimates. Model outcomes were subsequently calculated for alternative scenarios that simulated very different but realistic alternatives in parameter estimates, modeling, data handling, or analysis to obtain impressions of the total uncertainty. For the epidemiological assessment, 32 uncertainty sources were identified and for QMRA 67. Definitions (e.g., of a case) and study boundaries (e.g., of the studied pathogen) were identified as important drivers for the differences between the estimates of the original studies. The range in alternatively calculated estimates usually overlapped between disciplines, showing that proper appreciation of uncertainty can explain apparent differences between the initial estimates from both disciplines. Uncertainty was not estimated in the original QMRA studies and underestimated in the epidemiological studies. We advise to give appropriate attention to uncertainty in QMRA and epidemiological studies, even if only qualitatively, so that scientists and policymakers can interpret reported outcomes more correctly. Ideally, both disciplines are joined by merging their strong respective properties, leading to unified public health measures.

KEY WORDS: attribution; NUSAP; typology

1. INTRODUCTION

Campylobacter spp. and human campylobacteriosis have been studied extensively in the past decades, driven by their large disease burden and economic impact.[1–3] Studies were done in several scientific areas, including epidemiological assessments (EA) and quantitative microbiological risk assessment (QMRA), which relate directly to public health risks and its management. Studies from these two areas, although targeting the same research question (e.g., What is the number of campylobacteriosis cases due to chicken fillet consumption?), frequently provide results that differ substantially. These differences and contradictions pose a major challenge to public health policy. For instance, the annual *Campylobacter* incidence in the Netherlands from a population-based cohort study (EA) mounts to an estimated incidence of about 90,600 *Campylobacter* cases per year,[4] whereas a risk assessment study (QMRA) exploring 31 potential transmission routes estimates that 4.6 million *Campylobacter*

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cases occur in the Netherlands annually.[5] Furthermore, source and pathway attribution, which is a tool for prioritizing intervention measures to address the most important risk factors, is approached differently between disciplines and leads to different conclusions.[5,6] Insight into the factors causing these differences is required to aid proper policy development for disease burden reduction.

A predominant difference between foodborne disease EA and QMRA is the starting point in the *Campylobacter* transmission chain: EA studies the chain from human cases backwards to the causal factors (top down), whereas QMRA approaches the chain from the sources forwards to human cases (bottom up). Therefore, EA is in its final results mostly descriptive of what was observed, whereas QMRA is used both retrospectively as well as predictively for future health status. EA relies often on case observations through surveillance and on estimated multipliers to correct for underreporting, underascertainment, and selection bias. Furthermore, results from observational studies might be affected by recall bias, selection bias, or confounding.[7] QMRA in turn often faces poor data availability and therefore necessarily relies on assumptions. Furthermore, limited data are available to characterize dose-response relations adequately to allow extrapolation to low doses or other populations.[8] Given this different research approach, differences in uncertainties and contexts thus occur. Identifying these differences in uncertainties and contexts will help to identify the major differences that underlie the discordant results between EA and QMRA.

A structured approach for a discordance analysis has been applied in other disciplines, such as environmental health sciences.[9] The approach presented by Knol *et al.*[9] is based on a broad definition of uncertainty that covers, amongst others, statistical uncertainty, population variation, study boundaries and limitations, and choices made in modeling. Each of these uncertainty sources accounts for part of the total uncertainty that is ultimately associated with the final estimate. By characterizing uncertainty sources, it is possible to identify the best way to deal with the uncertainty in the study outcome. One approach that simultaneously addresses quantitative and qualitative aspects of uncertainty is NUSAP, which is an acronym for numeral, unit, spread, assessment, and pedigree, and that enables quantitative and qualitative assessment of the effect of uncertainty sources.[10] The approach is intended to characterize uncertainty sources based on their scientific rigor and to assess their relative importance on the outcome of interest. Combining these two aspects helps to identify the most important uncertainty sources—those with little scientific rigor and large influence on the outcome.

The aim of this article is to understand differences in outcomes between EA and QMRA that relate to campylobacteriosis in the Netherlands. To this end, we characterize the uncertainty sources of four previously published studies (two for EA and two for QMRA) by using an uncertainty typology as presented in Knol *et al.*[9] and elements of NUSAP as presented by Boone *et al.*[11,12] The differences between EA and QMRA approaches are examined for (i) the estimated annual incidence, (ii) the source attribution, and (iii) annual incidence for one particular source, that is, chicken fillet (Fig. 1). We subsequently quantified a larger part of the total uncertainty for the outcomes than originally presented by calculating outcomes for a number of plausible alternative scenarios.

2. METHODS

2.1. Uncertainty Typology

Uncertainties in model studies are diverse in form, and uncertainty typologies can help to structure these.[13] We identified the uncertainty sources by thoroughly reviewing the approaches used in the original studies, through reading the papers and reports (see Section 2.3) and discussions with scientists involved in the original studies. The uncertainty typology we subsequently used was based on Knol *et al.*[9] Uncertainties are characterized in the following dimensions (Table I): location (either contextual, model, or data uncertainty), nature (lack of complete knowledge, i.e., epistemic uncertainty, or system variability, i.e., ontic uncertainty), range (statistical or scenario based), methodological unreliability (either present or absent), and value diversity (either present or absent). Recognized ignorance, a dimension used by Knol *et al.*[9] to identify the recognition of ignored aspects in a study, was not considered to provide added value for the comparison of uncertainty sources between QMRA and EA and therefore not used. Table I lists the different uncertainty characteristics and provides examples specific for the studies focused upon in the current setting. Fig. 2 explains the concept of contextual uncertainty.

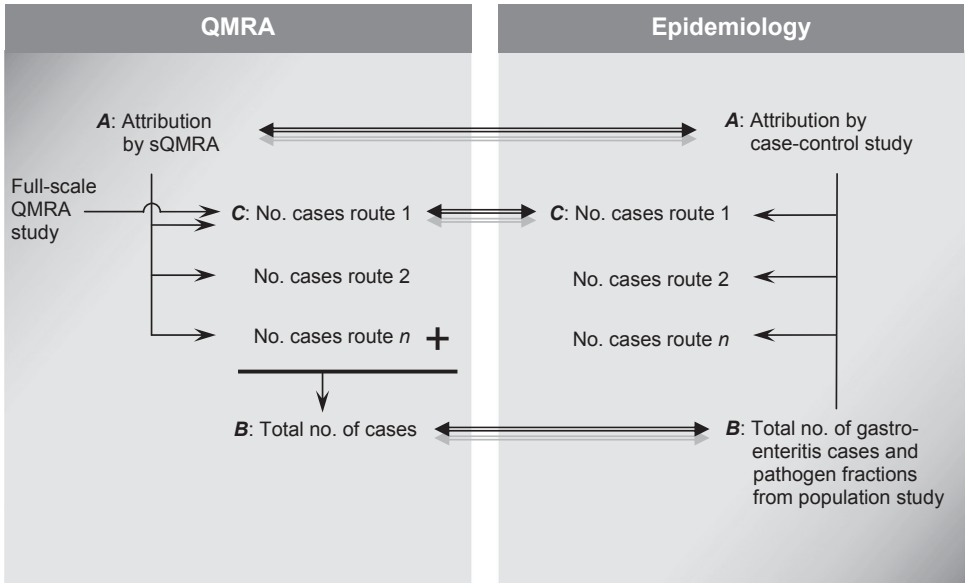

Fig. 1. Different calculation results that can be compared between QMRA and EA (double lined arrows) for *Campylobacter* in this study. Solid arrows indicate calculations within the disciplines. A simplified QMRA (sQMRA, or comparative risk assessment) can be conducted for all important transmission routes, thus estimating attribution (A), and the result of this can be summed to estimate the total number of cases for this pathogen (B). The more reliable estimated number of cases as calculated by full-scale QMRA (C) is typically only available for one transmission route (e.g., a specific food product, route 1). In EA, gastroenteritis population studies combined with laboratory surveillance data can give an estimate of this same total number of cases (B). This can be attributed to different transmission routes by, for example, case-control studies (A), and (A) can be combined with (B) to obtain estimated numbers of cases for specific routes, in this example for route 1 (C).

2.2. Ranking of Uncertainty Sources

The NUSAP approach[10] was used to rank all uncertainty sources identified with the typology, based on their scientific rigor and their influence on the outcome, similar to Boone *et al.*[11,12,14] Two approaches were used: one for input data and parameters and one for model assumptions. In short, the scientific rigor of parameters, data, and assumptions, and the influence on the outcome were assessed on a five-point scale. Poor rigor and large influence were marked with "0," high rigor and low influence with "4." For parameter and input data, the following criteria were used: the representativeness of parameters/data as proxy for the desired quantity (from exact measure to not correlated), empirical basis (from large sample size to a single observation or opinion), methodological rigor of the approach (from best available method to no discernible rigor), and degree of validation of the estimate (validation from independent observations to no validation). For model assumptions, the following criteria were used: influence of situational limitations (from hardly any influence to totally different assumptions), plausibility (from very plausible to fictive/speculative), choice space (from hardly any alternative to ample choice from alternatives), and agreement among peers (from large agreement to hardly any agreement).

The median score for rigor and the influence on results of each uncertainty source were plotted in a strength-effect diagram.[15] Uncertainty sources closest, in linear distance, to the X,Y coordinate (0, 0) were considered high-priority sources. The top three to six, a number chosen by the authors for practical reasons and depending on the study, were subsequently used in a procedure to get an impression of the magnitude of the total uncertainty of estimates from QMRA and EA (see Section 2.4).

2.3 Quantification of Influence of Top-Ranked Uncertainty Sources on Model Outputs

2.3.1. Total Incidence Estimation

2.3.1.1. Original QMRA study. In the QMRA approach, the number of campylobacteriosis cases and the source attribution is taken from a straightforward exposure assessment using an existing general transmission model (GTM) as presented in Evers *et al.*[5]

Table I. Description of the Uncertainty Typology Used to Characterize the Uncertainty Sources for Four Studies on *Campylobacter* spp. in the Netherlands, and Clarifying Examples; Modified from Knol *et al.*,[9] Each Uncertainty Source Is Characterized by Assigning a Designation for Each of the Dimensions (Italicized in the First Column)

Dimension	Explanation (examples)
Location	
Contextual	Related to choices on system boundaries and definitions (Case definition; year and place of data collection; strain under study; transmission routes included)
Model	Related to the causal structure chosen to model the system (Linear/nonlinear model; assumed distributions; additive/multiplicative model)
Data	(Related to parameters and raw data on which parameterization of the model is based) (*Campylobacter* counts on chicken fillet; number of observed cases; data sources used for standardization)
Nature	
Lack of complete knowledge	Related to incomplete knowledge associated with the uncertainty source (epistemic uncertainty) (Incidence estimate based on a sample, *Campylobacter* concentration on chicken filet based on a sample)
System variability	Related to variability in the system, outcomes can differ randomly (ontic uncertainty) (*Campylobacter* concentrations; host susceptibility to infection)
Range	
Statistical	Related to the possibility of expressing uncertainty in statistical terms as centralized estimate and interval (Mean and 95% interval for estimates)
Scenario	Related to the possibility of expressing uncertainty in a range of possible events (In-/exclusion of transmission routes; in-/exclusion of risk factors; alternative case definitions)
Methodological	Related to methodological weaknesses in the model or data (scored as present or absent)
Unreliability	(Present for: questionable estimation procedure, imperfect diagnostic tests that affects accuracy of results)
Value diversity	Related to subjectivity in choices made in the modeling (scored as present or absent) (Present when: peers can disagree with the approach related to the uncertainty source or when choosing between alternative models)

Human exposure is calculated as the mean number of campylobacters ingested per person per day (*D)* for 31 transmission routes (food, direct contact, and water routes) using a set of basic formulas. The formula for food routes was:

$$D_i = W_i \times P_{f,i} \times c_i \times f_i, \quad (1)$$

with W being the grams per day of item (food, feces, or water, depending on transmission route) i ingested, P_f the proportion of contaminated food products, c the *Campylobacter* concentration in item (cfu/g), and f the proportion of cross-contamination in consumers' kitchens ($f = 1$ for raw products). Direct contact estimates for route i were all calculated similar to the following petting zoo example:

$$D_i = n_i \times 1/N \times P_{a,i} \times F_{a,i} \times \pi_i \times W_i \times c_i, \quad (2)$$

with n_i being the daily number of humans with direct contact potential, N the number of Dutch inhabitants, P_a the proportion of contaminated animals, F_a the frequency of contacts with animals per person per day, and π the probability of feces ingestion given contact with animals. Exposure estimation for all water routes i was calculated similar to the following recreational water example:

$$D_i = a_i \times F_{w,i} \times W_i \times c_i, \quad (3)$$

with a_i being the proportion of the population in the age category under estimation and F_w the visiting frequency. The model was parameterized by literature data, unpublished data, and estimates by the authors. The original endpoint of exposure was entered in this study in a beta-Poisson dose-response relation as described in Section 2.4.1 to estimate annual case numbers.

2.3.1.2. Alternative QMRA scenarios. We explored the influence of changing two modeling approaches, that is, the dose-response model and inclusion of variability. Furthermore, parameter values were adjusted to clearly divergent but realistic values to assess uncertainty, which approaches the 95% intervals reported for EA estimates.

The alternative dose-response model replaced the beta-Poisson dose-response model with $\alpha = 0.145$ and $\beta = 7.589$,[16] estimated from data from a volunteer experiment reported by Black *et al.*,[17] with an exponential dose-response model fitted to the same data yielding an estimated infectivity, r, of 3.5×10^{-6}.[18] Variability was included by considering a lognormally distributed *Campylobacter* concentration (c_i from Equations (1)–(3)), with standard deviation taken as 10 times the arithmetic mean and

Table II. Risk Factors from CaSa and Transmission Routes from GTM That Were Compared in This Study for the Attribution of Transmission Routes to the Proportion of Campylobacteriosis Cases

CaSa risk factor	GTM equivalent
Chicken	Consumption of prepared chicken fillet and other raw and prepared chicken meat
Steak tartare	Raw beef consumption
Undercooked seafood	Consumption of prepared fish from fisheries, shellfish, and crustaceans
All foods[a]	All foods[b]
Ownership of dogs	Petting of dogs
Ownership cats	Petting of cats

[a]Including consumption of chicken fillet, consumption of steak tartare, consumption of meat prepared at a barbecue, consumption of undercooked seafood, and eating in a restaurant.
[b]Including all food routes.

truncated at a concentration of 10^{10} cfu/g, corresponding with the data-derived parameter values given in Nauta *et al.*[19]

Parameter scenarios involved alternative values for the scale parameter β of the beta-Poisson dose-response model, the amount of feces and water ingested (W_i in Equations (2) and (3)), and the fraction of *Campylobacter* transmitted via cross-contamination (f_i in Equation (1)). As alternative values for β in the dose-response model, the 95% confidence limits were used: 87.33 and 0.08348. Feces ingestion for direct contact transmission routes was changed 1 $\log_{10}$ unit bilaterally, the fraction of campylobacters transmitted via cross-contamination given a heated product (food transmission routes) was divided or multiplied by 31.6, and water intake via swimming pools and recreational water was divided or multiplied by 3.16. These values are equal to the data-availability-driven author estimates of uncertainty used in Evers *et al.*[5]

Alternative outcomes were assessed through MC simulation with 50,000 iterations, giving reasonable reproducibility as judged from five pilot runs (i.e., <1% deviation).

2.3.1.3. Original EA study. Annual incidence rates for campylobacteriosis in the Netherlands are estimated from a prospective population-based cohort study "SENSOR" done in 1998 and 1999 in the Netherlands.[20] Subjects were followed in two consecutive cohorts of each six months. An age-stratified random sample of 11,569 registrants at 27 (cohort 1) and 34 (cohort 2) Dutch general practices (0.5% and 0.7%, respectively, of all practices in the Netherlands) were requested to participate. In total, 4,860 persons participated and reported any development of gastroenteritis (GE). Feces of a subgroup of this study population were tested for causative agents in a nested case-control study. In total, 1,050 GE episodes occurred and the incidence, $P(GE)$, standardized for age, gender, and cohort, was estimated at 283 per 1,000 person-years with frequentistic Poisson regression analyses. In the nested case-control study, 9 of 700 cases (1.3%) and 4 of 665 controls (0.6%) excreted viable *Campylobacter spp.* in their feces. The standardized (for age, gender, and cohort) probability of *campylobacteriosis* given GE, $P(C|GE)$, was 2%. In a population of 15.8 million Dutch inhabitants in 1999, the incidence and attribution estimates lead to a total estimated incidence of campylobacteriosis cases of approximately 90,600 (95% interval 80,000–100,000 based on the reported uncertainty in the incidence estimate) per year.

2.3.1.4. Alternative EA scenarios. We explored the following alternative model scenarios for EA: inclusion of uncertainty for the proportion of *Campylobacter* cases among all GE cases, using Bayesian statistics as opposed to frequentistic statistics for $P(GE)$ and $P(C|GE)$, changing the prior for $P(GE)$ and $P(C|GE)$ in the Bayesian setting, introduction of age stratification as specific age groups are at particular risk,[21] inclusion of variability in the predictions of case numbers, and accounting for the *Campylobacter* excretors among the control group in SENSOR's nested case-control study. The effect of these uncertainty sources was assessed with Monte Carlo sampling (10,000 iterations) in @Risk (Palisade Software, Ithaca, NY, USA). The scenarios were examined jointly where possible (e.g., scenarios based on frequentistic and Bayesian statistics cannot be combined), leading to 25 alternative outcomes. The joint probability distribution of the outcome was considered a measure for parameter uncertainty,

Table III. Priority Uncertainty Sources for the Assumptions in the QMRA and EA Studies; the Characteristics of Identified Uncertainty Sources Are Indicated in the "Typology" Column, in the Following Order of Dimensions: Location (Contextual, Model, Parameters & Input Data), Nature (Epistemic, Ontic), Range (Statistical, Scenario); Methodological Unreliability (Plus/Minus); and Value Diversity (Plus/Minus); See Table I for an Explanation of the Uncertainty Dimensions; Each Source Was Subsequently Scored on Four Criteria (Columns 3–6) to Indicate its Scientific Rigor (0–4 = Low to High Rigor) and its Influence on Results (0–4 = High to Low Influence); the "Median" Column Displays the Median Score of the Rigor Assessment; Sources with a Low Median and Influence Score Are Considered High-Priority Sources

Subject	Typology	Infl. sit. lim.[a]	Plausibility	Choice space	Peer agreement	Median	Infl. on results
General transmission model							
Variability in time, place, and persons is not included for variables	mod, o, sc, –, +	1	1	1	2	**1**	**2**
Beta-Poisson dose-response model is adequate to describe human infection risks for ingested doses	mod, o, sc, –, +	4	2	2	2	**2**	**0**
CARMA study							
The mean concentration of *Campylobacter* in feces is lognormally distributed between flocks	mod, o, sc, +, +	4	2	0	3	**2.5**	**0**
The mean concentration of *Campylobacter* on the exterior is lognormally distributed between flocks	mod, o, sc, +, +	4	2	0	3	**2.5**	**0**
Different dose-response models that are not validated at low doses are available, while estimated doses are low	mod, o, sc, +, +	4	2	2	2	**2**	**0**
SENSOR study							
Case definition ("at least three loose stools in 24h, three vomit events in 24h or diarrhea with ≥2 additional symptoms") can cause very mild infections not to be included in the study (i.e., underestimation of incidence)	con, e, sc, –, +	4	1	2	2	**2**	**2**
The considered uncertainty is statistical (Poisson) uncertainty	mod, e, sc, +, +	4	1	2	3	**2.5**	**1**
CaSa study							
It is assumed that all exposure routes are included (yet the questions on the questionnaire are finite)	con, e, sc, +, +	1	2	1	2	**1.5**	**2**
Correlations between exposure routes (e.g., a particular sequence of exposures) are unknown and cannot be modeled	mod, e, st, +, –	1	1	4	3	**2**	**1**
Recall bias has no effect on the estimates	mod, e, sc, +, –	0	1	4	3	**2**	**0**
The sample size generated determines the statistical power	mod, e, st, +, –	1	1	4	3	**2**	**1**

[a]Influence of situational limitations.

Table IV. Priority Uncertainty Sources for the Parameters in the QMRA and EA Studies; the Characteristics of Identified Uncertainty Sources Are Indicated in the "Typology" Column, in the Following Order of Dimensions: Location (Contextual, Model, Parameters & Input Data), Nature (Epistemic, Ontic), Range (Statistical, Scenario); Methodological Unreliability (Plus/Minus); and Value Diversity (Plus/Minus); See Table I for an Explanation of the Uncertainty Dimensions; Each Source Was Subsequently Scored on Four Criteria (Columns 3–6) to Indicate its Scientific Rigor (0–4 = Low to High Rigor) and its Influence on Results (0–4 = High to Low Influence); the "Median" Column Displays the Median Score of the Rigor Assessment; Sources with a Low Median and Influence Score Are Considered High-Priority Sources

Subject	Typology	Proxy	Empirical Basis	Methodological Rigor	Validation	Median	Infl. on Results
General transmission model							
Response described by dose-response parameters might not be representative for the Dutch population (the issue of immunity)	par, o, sc, –, –	2	3	3	0	**2.5**	**0**
The same intensity of cross-contamination is used for all food categories and based on chicken preparation data	par, e, sc, –, +	1	2	3	0	**1.5**	**1**
Several factors for direct contact, incl. contact frequency, probability of contact with feces, and amount of feces ingested	par, e, st, +, –	4	1	1	0	**1**	**1**
Amount of water ingested during water recreation	par, e, st, +, –	4	1	1	0	**1**	**2**
CARMA study							
Parameter values by expert judgment (median of means) for defeathering and cutting	par, e, st, +, +	4	2	2	0	**2**	**1**
Parameter values for the cutting model are provided by one expert	par, e, st, +, +	4	1	2	0	**1.5**	**0**
It is assumed that chicken breast fillet is cut before the salad in 50% of the prepared meals	par, e st, +, +	4	0	1	0	**0.5**	**3**
SENSOR study							
The estimate for campylobacteriosis is based on nine observed cases	par, e, st, +, +	2	1	3	0	**1.5**	**0**
Period of concern is 1998–1999 and, e.g., implemented intervention measures could have changed the system	con, e, sc, –, –	2	2	3	0	**2**	**1**
The study population is a subset of the total population (e.g., no effect of voluntary participation or incomplete coverage of RPHL)	con, e, sc, +, –	2	2	3	0	**2**	**1**
CaSa study							
The selection procedure of cases leads to a possibly biased subset compared to all campylobacteriosis cases in the population	par, e, st, +, -	2	2	3	0	**2**	**0**

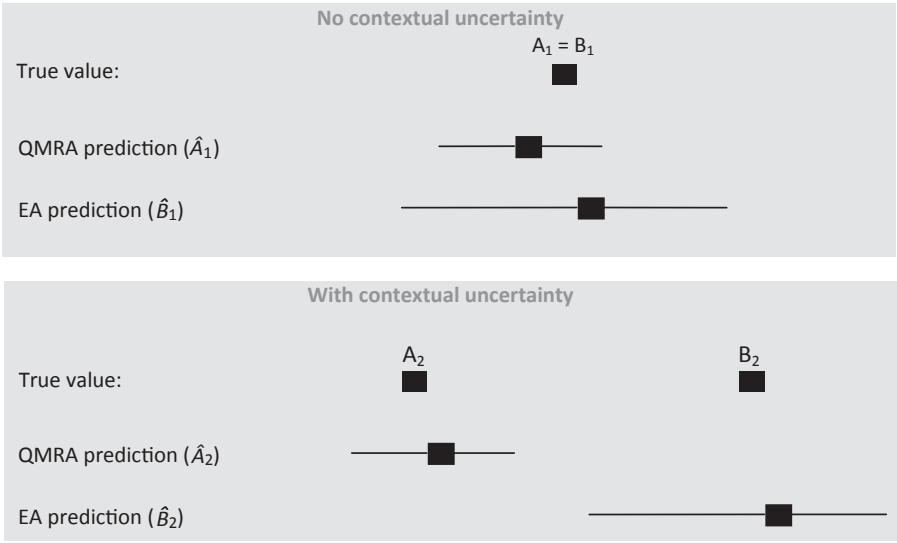

Fig. 2. Comparison between QMRA and EA models and the variables that are estimated, without and with contextual uncertainty (e.g., different definition of study boundaries in each discipline).

similar to the parameter scenarios examined for QMRA.

The uncertainty for the proportion of *Campylobacter* cases among all GE cases was estimated by binomial regression for the crude $P(C|GE)$ of 1.3% as data for reproducing the standardized estimate of 2% were unavailable. The 95% interval of the estimate was assessed by MCMC sampling directly from the likelihood function with the Metropolis-Hästings algorithm.[22] A prior for the parameter was not included, the burn-in was set at 1,000 interations, and the chain was run for 10,000 accepted realizations at an acceptance rate of 35–40%. The subsequent MCMC posterior was described with a beta-distribution from which values were sampled in the scenario analyses.

Havelaar *et al.*[23] estimated $P(GE)$ and $P(C|GE)$ from the SENSOR data, using Bayesian statistics. The uncertainty of $P(GE)$ was described by a Gamma(κ, ϑ) distribution, with κ being the number of GE cases or campylobacteriosis cases among GE cases and ϑ the reciprocal of the time at risk as observed in SENSOR.[24] The uncertainty of $P(C|GE)$ was described by a beta (k, n) distribution, with k being the number of campylobacteriosis cases in the nested case-control study and n the number of controls. A prior distribution beta (0.15, 4) was used to emphasize an infection probability <0.25 with 95% probability, yielding beta ($k + 0.15$, $n - k + 4$) distributions for the uncertainty of $P(C|GE)$ from which values were samples in the scenario analyses.

The effect of the prior beta (0.15, 4) was examined by adjusting the prior distribution to a beta(1, 1). This prior considers each value between 0 and 1 evenly likely, with an average probability of 50%.

The age stratification was included in the frequentistic and Bayesian approaches described above. In the latter, six age classes were discerned.[23] The nine cases excreting *Campylobacter* were distributed as follows: 0 ($n = 1$ of 197), 1–4 ($n = 4$ of 267), 5–11 ($n = 3$ of 128), 12–17 ($n = 0$ of 19), 18–64 ($n = 1$ of 57), and 65+ ($n = 0$ of 31). Because no campylobacteriosis cases were observed in two of the six age classes, the frequentistic approach discerned two age classes: individuals <12 years of age and those ≥ 12 years. This age stratification was also used in one of the scenarios with the Bayesian approach.

Variability was included in the Bayesian setting only, for the number of *Campylobacter* excretors among the GE cases. For each of the six age classes a random number of *Campylobacter* excretors was sampled each iteration from a binomial(n, p) distribution, with p being the proportion of *Campylobacter* excretors and n the number of GE cases per age class. The newly simulated number of *Campylobacter* cases was subsequently used as k_i in the age-specific beta distributions described above (thereby combining uncertainty and variability in the outcome).

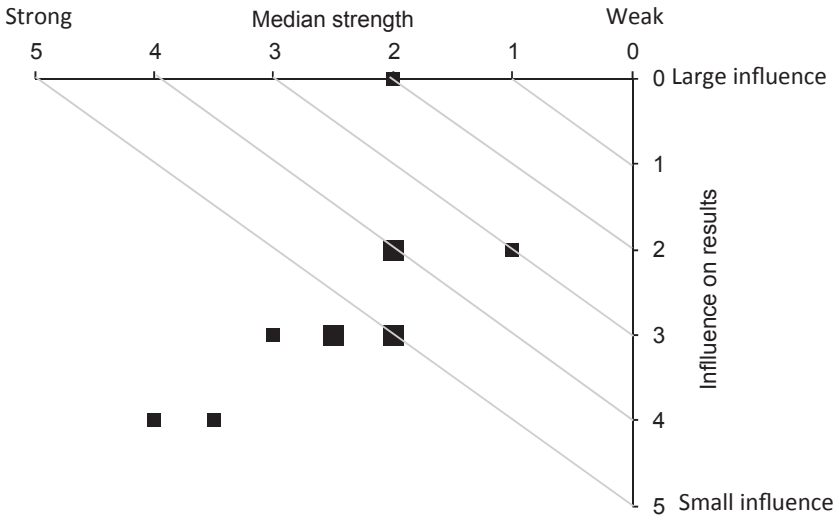

Fig. 3. Example of a strength-effect diagram of model structure uncertainty, for the GTM model. Each marker represents an uncertainty source, with bigger markers representing two sources with the same score. Sources closest (in linear distance) to the origin (0, 0) are considered important uncertainty sources. The gray diagonals bound areas in which uncertainty sources were considered equally important.

Accounting for the 4 of 665 controls who excreted *Campylobacter* in their feces in the nested case-control study was done by describing this probability, $P(C|non\text{-}GE)$, with a beta distribution similarly to those used for $P(GE)$ and $P(C|GE)$, with $k = 4$, $n = 665$ and a prior distribution beta(0.15, 4). Two approaches were subsequently followed: one in which the total number of campylobacteriosis cases was increased by multiplying $P(C|non\text{-}GE)$ with the number of individuals in the Netherlands that is estimated to not develop GE; and another in which $P(C|non\text{-}GE)$ was subtracted from $P(C|GE)$ to correct the latter for a baseline level of asymptomatic cases. If $P(C|non\text{-}GE)$ exceeded $P(C|GE)$ in a particular iteration, then $P(C|GE)$ was set to zero.

2.3.2. Source Attribution

2.3.2.1. Original QMRA study. The source attribution by QMRA is based on the GTM described in Section 2.3.1.1. Percentages per transmission route are calculated as the number per route divided by the total number of cases estimated for all transmission routes.

2.3.2.2. Alternative QMRA scenarios. The alternative scenarios are those described in Section 2.3.1.2. Percentages per transmission route are calculated as the number per route divided by the total number of cases estimated for all transmission routes.

2.3.2.3. Original EA study. Data on source attribution for campylobacteriosis were taken from a case-control study done in 2003.[6] Cases were patients with a laboratory confirmed *Campylobacter* infection that were identified by the Regional Public Health Laboratories, covering about 50% of the Dutch population. Controls were selected based on historic case numbers from these laboratories stratified by age, gender, degree of urbanization, and season (i.e., frequency matching). In total, 1,315 *Campylobacter jejuni* cases were compared to 3,409 controls. Missing data for explanatory variables were handled using multiple imputation, by which five separate data sets were created. Explanatory variables with a p-value ≤ 0.10 in univariable logistic regression were analyzed in multivariable logistic regression. Variables were eliminated from the model until all p-values were ≤ 0.05. The most important exposure risk factors were the consumption of chicken (population attributable fraction (PAF): 28%), followed by consumption of meat prepared at a barbecue, grill, or microwave oven (12%) and eating in a restaurant (10%).[6]

2.3.2.4. Alternative EA scenarios. Three alternative scenarios for exploring the uncertainty related to the source attribution were examined: the method for assessing PAFs, the inclusion of variability in the PAF interval, and the effect of distinguishing *C. jejuni* from *Campylobacter coli* (which was not done in QMRA).

The PAFs can be calculated from the excess risk (i.e., due to the risk factor) of being a case, p_e, the number of exposed cases (E), and the total number

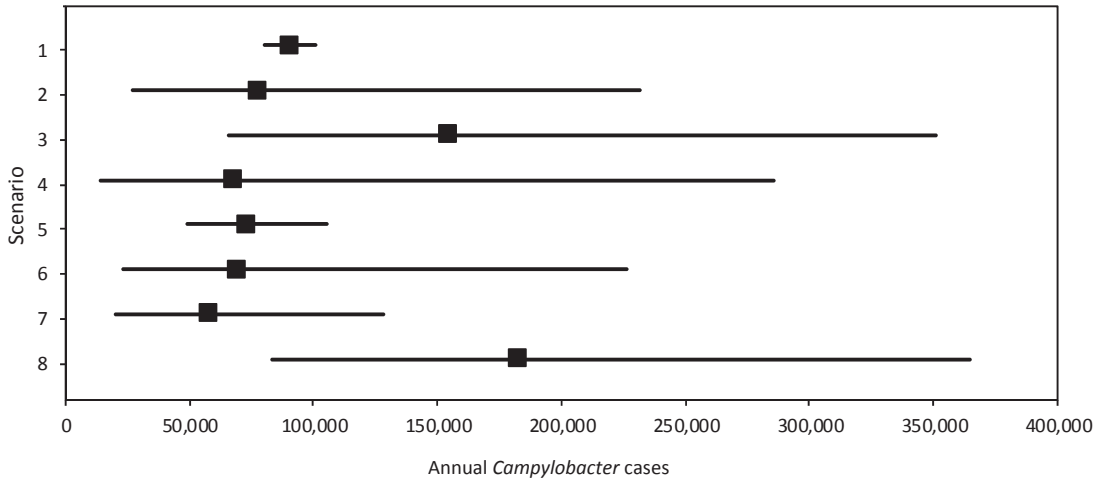

Fig. 4. Eight examples of alternative scenarios for estimation of the total campylobacteriosis incidence in the Netherlands, based on a population-based cohort study. The marker (■) indicates the median estimated number of cases from the MCMC sampling, the solid lines represent the 95% interval of the MCMC posterior. Scenario 1 is the baseline estimate, scenario 2 includes additional uncertainty in time at risk for gastroenteritis (GE) and conditional probability of campylobacteriosis given GE, scenario 3 is as scenario 2 with a noninformative prior for the conditional probability of campylobacteriosis given GE, scenario 4 is as scenario 2 with variability included, scenario 5 is based on a maximum likelihood estimate of the conditional probability of campylobacteriosis given GE without age effect, scenario 6 is as scenario 5 but with age-specific MLE estimates, scenario 7 is as scenario 2 with correcting for the four asymptomatic cases as if these respresent a baseline asymptomatic proportion, and scenario 8 is as scenario 2 with addition of the four asymptomatic cases in the nested case-control study of the population-based cohort study.

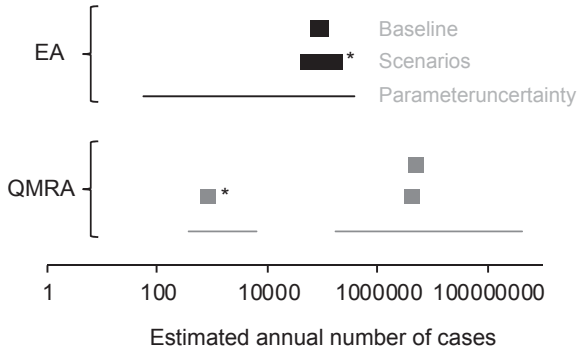

Fig. 5. Estimation of the annual total number of campylobacteriosis, for different alternative calculations, based on EA (■) or QMRA (■) . The top marker per discipline indicates the original estimate from the respective study. The scenario markers indicate the mean estimate of number of cases. The parameter uncertainty line indicates the uncertainty associated with the estimated number of cases.
*Several markers (25 for EA; 2 for QMRA) cover each other partly or entirely.

of cases (C) through:

$$PAF = p_e \frac{E}{C}. \tag{4}$$

In CaSa p_e and its 95% interval were estimated as $(OR - 1)/OR$. As an alternative, the regression estimates were used to calculate a reference risk p_{ref} from the model intercept β_0:

$$p_{\text{ref}} = (1 + e^{-\beta_0})^{-1}. \tag{5}$$

The p_e was subsequently calculated from this p_{ref} and the OR as:

$$p_e = (1 + e^{-\beta_0 + \ln OR})^{-1} - p_{\text{ref}}. \tag{6}$$

The associated 95% intervals were obtained by Monte Carlo simulation (10,000 iterations), using the normal distributions for the βs with $\hat{\beta}$ as mean and the standard error of $\hat{\beta}$ as standard deviation.

Variability was visualized in the 95% intervals of PAFs by considering the development of campylobacteriosis due to a risk factor as a random binomial process (yes/no infected after exposure). The p_e was taken as probability of "success" in a binomial trial, and the total number of exposed individuals was taken as the number of trials. The resulting number of excess cases was subsequently divided by the total number of cases (i.e., 1,019) to assess the PAF and its 95% interval

The third considered uncertainty source was the distinction between *C. jejuni* and *C. coli* that was

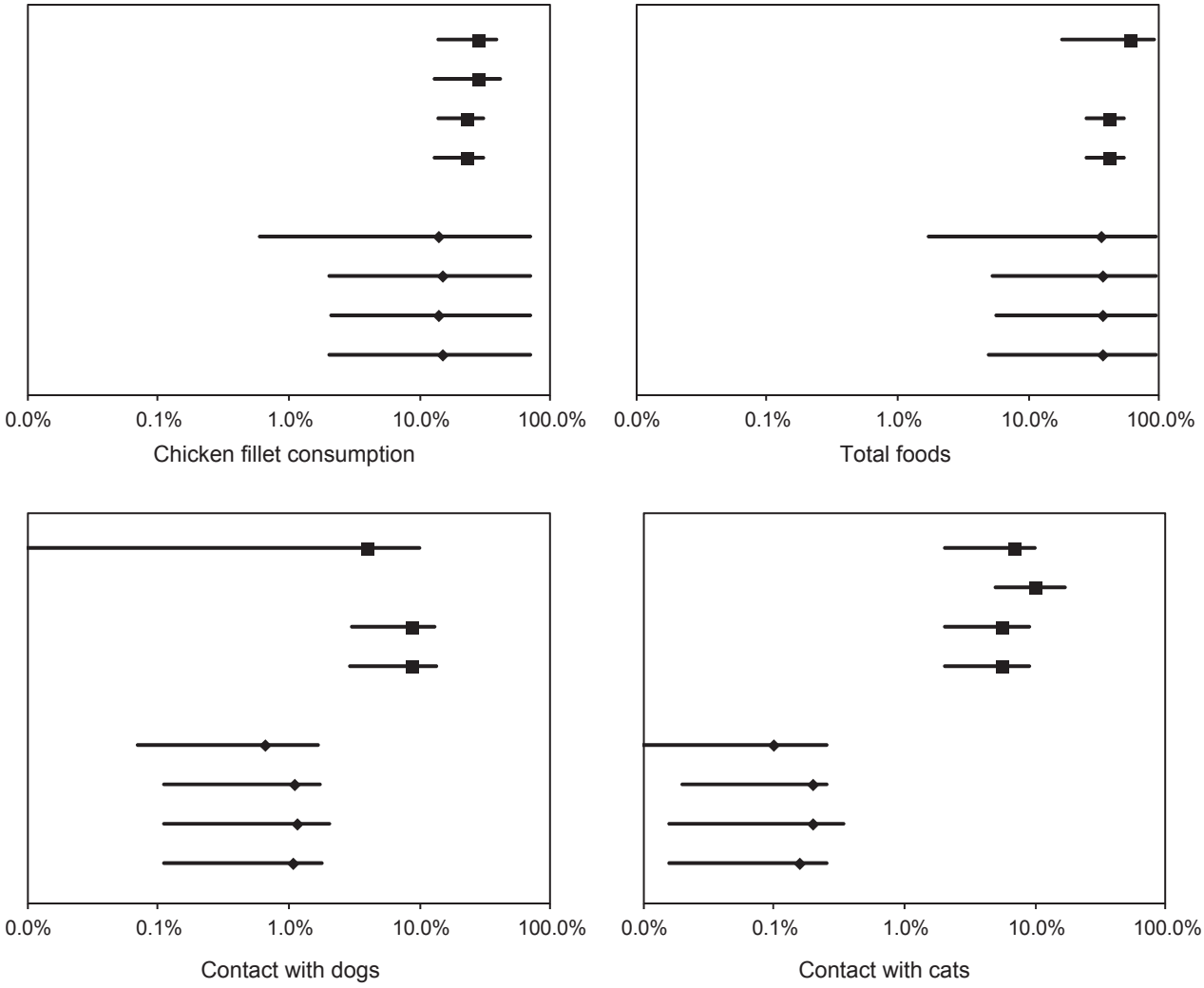

Fig. 6. Range of percentages of campylobacteriosis cases attributed to the sources explained on the *x*-axis label. The upper four ranges reflect epidemiological estimates (■), the bottom four QMRA estimates (♦). For EA, the upper range reflects the estimates based on CaSa data for *C. jejuni*,[6] the second range the estimates based on CaSa data for *C. jejuni* and *C. coli*,[25] the third range the estimates based on the regression model as explained in Section 2.4.6, and the fourth range is identical to the third with binomial variability included. For QMRA, the upper range reflects the baseline scenario with the beta-Poisson dose-response model, the second range the estimates based on the exponential dose-response model, the third range the estimates based on the beta-Poisson dose-response model with variability included, and the fourth range the estimates based on the exponential dose-response model with variability included.

originally made in CaSa and not with QMRA. Mughini Gras *et al.*[25] analyzed the original *C. jejuni* and *C. coli* data jointly. The PAF estimates from CaSa and latter study were compared to assess the effect of omitting or adding *C. coli*.

2.3.4. Incidence Estimation due to Chicken Fillet Consumption

2.3.4.1. Original QMRA study. The number of campylobacteriosis cases related specifically to chicken fillet is estimated by the QMRA models developed in the CAmpylobacter Risk Management and Assessment project (CARMA),[26] with the models described by Katsma *et al.*,[27] Mylius *et al.*,[28] and Nauta *et al.*[19,29] The proportion of contaminated birds per flock on farms as modeled with a SIR-model and count data of *Campylobacter* on the birds' exterior and in the feces were used as input for a model describing the slaughterhouse processes, the cutting stage, the storage stage, and the preparation by consumers. The original study considered

only exposure of humans to *Campylobacter* due to cross-contamination in the kitchen as heating of fillets was considered to inactivate *Campylobacter* completely. The model takes into account the number of table companions. The number of cases is calculated subsequently from the estimated exposure using a beta-binomial dose-response model.

The CARMA model consists of a processing model and a consumer model. A set of 5,000 iterations, simulating 5,000 flocks of chickens, was used in this study for the processing model. The resulting values were input for the consumer model that consisted of 100,000 iterations, sampling 20 fillets from the distribution of each flock for the 5,000 flocks as done by Nauta *et al.*[19]

2.3.4.2. Alternative QMRA scenarios. We explored the influence of changing two modeling approaches: the dose-response model and exclusion of variability. Furthermore, parameter values were adjusted to clearly divergent but realistic values for three parameters: the expected proportion of campylobacters transmitted via cross-contamination, the probability per *Campylobacter* to move from the environment to the carcass exterior (b_{env}), and the proportion of consumers that cuts the chicken fillet before salad preparation.

The original CARMA model uses the beta-binomial dose-response model to estimate infection risks.[19] As alternative scenario, the exponential dose-response model as described in Section 2.3.1.2, was used.

Variability was included in the original CARMA model in the mean concentration of *Campylobacter* in feces and on the exterior (lognormally distributed between flocks). The alternative scenario considered the extreme scenario of absence of variation between flocks. The flock means of the $\log_{10}$ *Campylobacter* concentration per gram feces were normally distributed with mean 5 and standard deviation 1.52 in the base scenario. The alternative scenario uses a constant value of 8.66 $\log_{10}$ campylobacters per gram feces. Similarly, the flock-means of the $\log_{10}$ *Campylobacter* number on the whole carcass exterior were considered normally distributed (mean: 7.27; *SD*: 0.83) and the alternative scenario constant value was 8.06 $\log_{10}$ campylobacters. Note that the alternative mean values are higher than the base scenario $\log_{10}$ mean value of the normal distributions.

In the consumer preparation phase model, it was assumed originally that chicken breast fillet was cut prior to the salad in 50% of prepared meals. In alternative scenarios, this level was set to 10% and 90%.

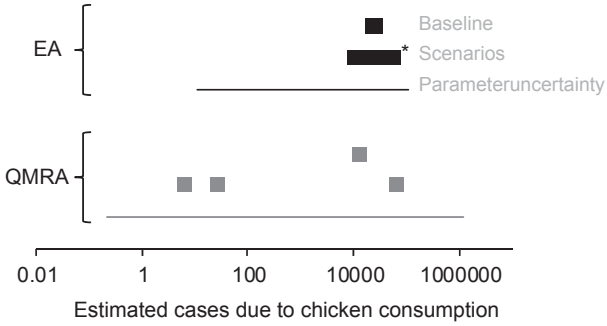

Fig. 7. Estimation of the annual number of campylobacteriosis cases due to chicken consumption, for different alternative calculations, based on EA (■) or QMRA (■) . The top marker per discipline indicates the estimate based on the original studies. The scenario markers indicate the mean estimate of number of cases. The parameter uncertainty line indicates the uncertainty that was associated with the estimated number of cases.
*Forty-nine markers cover each other partly or entirely.

In the cutting stage model of CARMA, the expected proportion of campylobacters transmitted by cross-contamination from breast cap and environment to the fillet was changed from –1.8 $\log_{10}$ value to –2.3 or –1.3, as done in the sensitivity analysis by Nauta *et al.*[19]

In the slaughter stage model, eight parameters, each with slaughter-stage-specific values, were based on expert judgment.[30] The most influential of these eight parameters was used in the scenario analyses of this study. This parameter was identified by assessing, separately for each parameter for all slaughter stages, the change in outcome after entering the 5 and 95 percentiles, which were also estimated in the expert study. The parameter b_{env} was found to have the largest effect on the outcome. This parameter describes the probability per cfu *Campylobacter* from the environment to move to the carcass exterior.

2.3.4.3. Original EA study. The number of cases associated with the consumption of chicken fillet was estimated by combining the standardized incidence estimate of 282 per 1,000 person-years from SENSOR (see Section 2.3.1.3) with the PAF of 28% from CaSa (see Section 2.3.3.3).

2.3.4.4. Alternative EA scenarios. The estimated total incidence of campylobacteriosis was estimated

using the 25 different alternatives as described in Section 2.3.1.4 and the two different approaches for estimating the PAF as described in Section 2.3.3.4. The incidence due to chicken fillet was obtained by multiplying the PAF estimate with the number of cases. This approach led to 50 alternative calculations in total.

2.4. Comparison of the Uncertainty of Model Outputs from QMRA and EA

Comparison of the uncertainty between the two disciplines is not straightforward and needs to be done with the proper reservations. The results cannot be used to compare the quality of the disciplines in general. This is important to understand and therefore mentioned here. The topic will be further covered in the discussion Section 4.

Comparisons between the estimates from both disciplines were based on the median estimate per scenario and on the range due to parameter uncertainty (QMRA) or statistical uncertainty (EA). In case of overlapping ranges, the estimates were considered not different.

3. RESULTS

3.1. Identification and Characterization of Uncertainty Sources

For QMRA, the analysis of the GTM led to the characterization of 34 uncertainty sources, those of CARMA to 33 uncertainty sources. For EA, 12 uncertainty sources were identified in the SENSOR study, and 20 for the CaSa study. All results from applying the typology are available upon request from the corresponding author. The uncertainty sources for QMRA were caused by lack of complete knowledge and system variability, whereas the sources for EA were all caused by lack of complete knowledge.

Part Some of the risk factors determined by the CaSa case-control study were not compatible with the GTM approach. This source of uncertainty can be characterized as contextual uncertainty and was noted as a potentially important driver for differences in the final estimates between the two disciplines. In the quantitative uncertainty analyses, those factors that were similar between the studies were further examined (Table II).

3.2. Ranking of Uncertainty Sources

The top-five most important uncertainty sources are displayed in Tables III and IV for the assumptions and parameters, respectively. An example of a strength-effect diagram that was used for identifying these sources is shown in Fig. 3. All sources for QMRA were available for quantitative analyses of their effect on the total uncertainty. For the CaSa study, all sources related to assumptions and parameters (i.e., those in Tables III and IV) could not be analyzed quantitatively. Alternative uncertainty sources that were considered were: the effect of (not) distinguishing *C. jejuni* and *C. coli* and the inclusion of variability in the interval (see also Section 2.4.4). The uncertainty sources for SENSOR related to the case definition (Table III) and parameter uncertainty (Table IV) except that the exclusion of uncertainty other than statistical uncertainty in the Poisson regression could not be analyzed quantitatively. The five sources that were examined are explained in Section 2.4.2.

3.3. Effect of Uncertainty Sources on Estimates and Intervals

3.3.1. Total Campylobacteriosis Incidence

Fig. 4 shows the results of eight different scenarios for EA, with the marker as mean estimate number of cases and the line representing the 95% statistical interval. This interval consists of the lowest 2.5% lower limit and highest 97.5% upper limit of the 95% intervals per estimate. These 2.5% and 97.5% limits display the doubt one has about the value for the estimated parameter, given the analysis approach and the assumed probability distribution for the parameter. Fig. 5 shows the range in all estimates for EA and QMRA. Note that the scenario for EA consists of the black line for the range in mean estimates, supplemented with the range in statistical 95% intervals as a gray line. For QMRA the line reflects the range in estimates given the scenarios due to parameter uncertainty. Classical statistical uncertainty estimates are not included in QMRA analysis.

The median estimated number of cases for EA varied between 45,000 and 200,000, with the lowest 2.5% limit and largest 97.5% limit at 59 and 374,000, respectively. The largest 95% interval for a single scenario, from 42,000 to 325,000, was observed for the scenario in which the beta(0.15, 4) prior was changed to beta(1, 1) and binomial

variability in number of campylobacteriosis cases was included.

For QMRA, the effect of uncertainty sources on the estimated mean number of campylobacteriosis cases was examined in 27 or 81 (a base, low, and high scenario for three or four parameters, i.e., 3^3 or 3^4) parameter scenarios for each of four model scenarios (Fig. 5). The value for the base model scenario is 4.9×10^6 cases, the minimum and maximum due to parameter scenarios are 1.8×10^5 and 5.9×10^8. The parameter β of the beta-Poisson dose-response model was most influential for the parameter scenarios, and the type of dose-response model for the model scenarios. Inclusion of variability (a model scenario) did not affect the range in parameter scenario estimates.

3.3.2. Source Attribution

The attribution values for consumption of chicken fillet, for total food consumption, and for ownerships (EA) or petting (QMRA) of cats and dogs are given as an example in Fig. 6. In the epidemiological studies, differences in percentage of attribution did not vary to a large extent among the examined scenarios. Estimation of the PAF based on the regression estimates was structurally marginally lower than compared to estimates based on the OR. The inclusion of variability in the prediction intervals for the PAF did not lead to an increase.

The attribution to chicken gave a large variation as a function of the parameter scenarios in QMRA from 0.6% to 69%. Dominant factors driving the estimate were cross-contamination of foods and feces ingestion due to direct contact: low levels of direct contact ingestion combined with high levels of cross-contamination give the highest 9 chicken attribution values and high direct contact ingestion combined with low or base cross-contamination gives the lowest 18 chicken attribution values.

The ranges in estimated proportions overlapped between QMRA and EA for the consumption of chicken fillet, consumption of steak tartar, the ownership/petting of dogs, for consumption of undercooked seafoods (albeit barely), and for total food-related exposures; the ranges did not overlap for the ownership/petting of cats.

3.3.3. Campylobacteriosis Incidence due to Chicken Fillet Consumption

The estimated incidence of chicken fillet consumption based on the epidemiological studies was comparable to the estimates from CARMA in the baseline model (Fig. 7). The PAF estimations based on regression predictions were structurally marginally lower than predictions based on the estimated OR. The interval between lowest 2.5% limit and largest 97.5% limit ranged from 15 to 109,000 for the estimates based on OR and from 11 to 81,000 for estimates based on the regression model.

The predicted number of cases due to chicken fillet consumption for the 27 combinations of parameter values (low, base, and high for each of three parameter considered) for the baseline scenario of the CARMA study was 1.3×10^4 cases, and varied between scenarios from 8.1×10^2 to 2.5×10^5 (Fig. 7). No parameter uncertainty source is clearly dominant. The effect of changing the dose-response model into the exponential dose-response model ("expo"), excluding the variability in *Campylobacter* concentration in feces and on the exterior between flocks ("no flockvar"), and both is also presented in Fig. 7. Overall, the number of cases varied between 2.2×10^{-1} and 1.2×10^6. The dose-response model is dominant for the uncertainty between models: using the exponential dose-response model reduces the median with a factor of about 1.4×10^3 compared to the beta-Poisson model, whereas exclusion of variability in mean *Campylobacter* concentrations on exterior and in feces between flocks increases the median with a factor of about 4.5 compared to scenarios with variability. The largest difference between medians is a factor 6.2×10^3, between "expo" and "no flockvar."

4. DISCUSSION

Differences between epidemiological studies and QMRA models that apparently target the same pathogen and transmission routes may differ substantially, troubling policymakers to a large extent. This study aimed to identify and quantify as much as possible the total uncertainty for estimates based on QMRA and EA for the *Campylobacter* spp. incidence and source attribution in the Netherlands. Structured identification of uncertainty sources, and simulation using different analyses approaches than used in the initial studies, gave insight into the differences and similarities between EA and QMRA. Furthermore, the choice of analysis approach and uncertainty sources to include in presented intervals was shown to potentially affect results by several orders of magnitude. We advise here to give more

attention to uncertainty, even if only qualitative, in future QMRA and epidemiological studies, so that scientists and policymakers can interpret analysis outputs in a correct way.

This study does not attempt to compare EA and QMRA in identifying the superior discipline and thereby present one best estimate of campylobacteriosis cases, although results are tempting to be used as such. First, there is no gold standard available of the true number of campylobacteriosis cases that could be used to valuate estimates from EA and QMRA. Second, given the different research approaches that are used by these disciplines, different uncertainty sources could be examined in the quantitative analysis. In general, QMRA studies represent sets of equations with particular, estimated or assumed, values for parameters. These values can be changed relatively easy to assess their effects on the outcome. This leads to a larger flexibility in scenario calculations for QMRA than for EA, and to possibly larger presented intervals. The EA studies that were used, and most epidemiological studies in general, are based on data that reflect past occurrences, that is, these represent a single outcome of many variable processes and circumstances that coincided. And regression techniques aim to estimate the mean value of parameters, with the presented interval indicating the uncertainty that is attributed to that value. Usually, additional data, such as answers to additional questions, is not available from the same study population, which limits the number of possibilities for quantitative uncertainty analyses in EA. We thus had to omit uncertainty sources in the quantitative analyses for EA more often than for QMRA. Third, the nature of uncertainties and approaches for quantification differ fundamentally between QMRA and EA in this study. Statistical uncertainty was included in the EA estimates and not in those for QMRA. Variability was included in QMRA estimates and not in those for EA. And fourth, it must be realized that QMRA is a recent discipline compared to EA. This implies poorer data availability and less-developed modeling techniques. All these aspects need to be realized when interpreting the results between QMRA and EA. We restricted our comparison to the estimated range of possible estimates (i.e, campylobacteriosis cases, attribution) given different realistic decisions and assumptions that could have been made in the initial studies. These ranges therefore include—albeit some with more likelihood than others—estimates that could have been presented to policymakers.

The application of the typology and NUSAP to identify the most important uncertainty sources showed that definitions and study boundaries are important drivers for the difference among estimates by EA and QMRA. For instance, case definitions differed between the QMRA model and the epidemiological counterpart, as did the initial different handling of *C. jejuni* and *C. coli*. Furthermore, geographical locations where, and time periods in which, data were collected differed and possibly led to differences in study estimates. These study boundaries relate to the contextual uncertainty, and were identified as the most important location of uncertainty in other studies.[9] Differences in contextual uncertainties are important for realization, but cannot be analyzed in quantitative analyses. Using NUSAP approaches, however, an impression of the magnitude of its effects can be assessed, as was done in this study.[10] The identification and characterization of uncertainty sources with a typology can assist in setting priorities for future research. The sources that reflect epistemic uncertainty are of particular interest for this because increasing measurements on the variable can reduce the amount of uncertainty.

Nonoverlapping uncertainty intervals of estimates from QMRA and EA were observed in this study and can be due to contextual uncertainty. The absence of an overlap can also be related to an underestimation of the actual data or model uncertainty, with or without the presence of contextual uncertainty. The cause of nonoverlapping intervals is thus difficult to ascertain at first sight, and a structural evaluation of the uncertainty sources is useful to find the most likely explanation. For instance, in this study the nonoverlapping confidence intervals as found for cats and dogs (Fig. 7) could well be due to contextual uncertainty, as the QMRA estimate is only based on the transmission route of directly touching the cat or dog, whereas the epidemiological estimate is based on the overall factor of ownership of dogs or cats.

Apart from existing contextual uncertainties that are present in study results, new uncertainty sources are added by extrapolation of results from published studies to a new context. Where, for instance, the original researchers might intend to estimate an incidence for period a in country A, other researchers might be driven to use these results for period b in country B due to, for example, lack of more specific data. This extrapolation evokes additional uncertainty in the extrapolated estimate compared to the original because the context changed. Including

this additional uncertainty is challenging and in cases impossible, but important to realize or have realized by a study audience.

The strength and effect evaluation as part of NUSAP was done in this study by the authors only. Preferably, such elicitation is based on a group of experts from various related research fields.[10] The advantage of a multiexpert elicitation, especially for one composed of experts from various adjacent scientific fields, is the inclusion of varying scientific arguments in the valuation of the pedigree criteria of uncertainty sources. The prioritization as presented in this study likely would have changed if a group of experts had been interviewed, but due to time limitations this was not done. Furthermore, despite efforts to approach the current analyses as objectively as possible, subjective choices still had to be made. In that respect, our results are also not without various sources of uncertainty. The current results regarding the prioritization of uncertainty sources should be interpreted as an initial exploration, rather than as confirmed prioritized sources guiding future research needs.

The dose-response model had the largest influence on the outcome of QMRA. This finding represents several aspects of uncertainty. First, the dose-response model establishes contextual uncertainty because the case definition is fixed to the case definition of the experimental study on which the dose-response model is based. Second, the statistically best-fitting dose-response model type (e.g., beta-Poisson, exponential, Weibull) is usually selected for estimating adverse health risks. The assumption that the dose dependency of health responses for the population to which the model is applied is identical to those of the dose-response study population is then required. Although the best way forward in the absence of more representative data, this assumption is almost always invalid. For instance, heterogeneity in acquired immunity to campylobacteriosis due to previous exposures is expected to have a large influence on the estimated case numbers at population level. A modeling study on the effect of immunity in dose-response modeling showed that a constant probability of illness given infection and ignoring the impact of acquired immunity yields unrealistically high estimated case numbers.[31] Such unrealistically high numbers were observed in several scenarios in this study. And third, next to model choice, the absolute values for the parameters of the dose-response model and their uncertainty are estimated from the experimental study and applied to the population under study. The latter two extrapolations simplify reality, as is desired with modeling, but this simplification leads to additional uncertainty that is usually not included in confidence intervals. Confidence intervals presented in literature therewith underrepresent the actual uncertainty related to the hazard quantification.

The uncertainty in the SENSOR study was especially related to the choices regarding the Bayesian prior and the decision to exclude the four *Campylobacter* excretors in the control group of the nested case-control study. The difference between lowest and highest median estimate was a factor of 3, whereas the lowest 2.5% lower limit and largest 97.5% upper limit differed by a factor of 26. For the CaSa study, limited variation in the outcome was observed in alternative scenarios. This finding might suggest that CaSa estimates are robust within the scenarios that we examined (note that the correctness of the estimates remains unknown). Nevertheless, the choice space for alternative scenarios was very limited and only few alternative scenarios could be examined. Potentially important uncertainty sources include the causality that is implied for the risk factors, data reliability, the data manipulation, and the modeling.

In addition, contextual uncertainties could not be quantified and might play an important role. For instance, eating chicken fillet *per se* is not the risk factor; it is either eating, or handling, chicken fillet that is contaminated by *Campylobacter*. Furthermore, as in QMRA, immunity might play a role in the output of EA, as frequent chicken fillet consumers might be more often exposed to *Campylobacters* and thus acquire immunity more frequently. Potential risk factors might then be identified as preventive factors. The effect of such uncertainty sources on the estimates is difficult to quantify and therefore not visible in the current analyses.

In conclusion, this study provides insight into the broader uncertainty of final estimates for campylobacteriosis incidence, source attribution, and *Campylobacter* incidence due to chicken consumption. By examining the range in potential outcomes and the associated 95% statistical confidence intervals for EA given different choices for the analyses, a larger part of the total uncertainty was visualized. On the one hand, differences in estimates can occur when there is difference due to contextual uncertainty between the two disciplines that is not masked by model and data uncertainty. On the other hand, most uncertainty intervals overlap, showing

that the apparent differences between QMRA and EA estimates that initiated this study are misleading. These apparent differences are possibly caused by not estimating the uncertainty (in the QMRA studies that we considered) or underestimating it (in the epidemiological studies). As both disciplines often aim at estimating the same health measure for the same pathogen, both approaches are ideally joined by merging the strong aspects of both disciplines. This will be examined as follow-up of this study.

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