Quantification of uncertainty in Quantitative Microbiological Risk Assessment by Bayesian calibration of multiple linked models

Master's Thesis

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Abstract

Bacterial outbreaks of Campylobacter caused by chicken consumption are becoming more frequent in Sweden during the hot season. Quantitative Microbiological Risk Assessment (QMRA) applied to Campylobacter contamination related to consuming chicken uses multiple models covering different stages ranging from primary food production to consumption. In this thesis a prevalence and concentration model is used and it covers the contamination of Campylobacter during the primary production. Another stage models is the Consumer Phase Models (CPM) which estimates the risk of cross-contamination when handling chicken in kitchen resulting in a dose bacteria being ingested. This dose can then be fed into a dose-response model to estimate the risk of illness from Campylobacter due to the ingested dose.

QMRA opens up for an explicit treatment of uncertainty, which can be divided into two types: aleatoric, due to inherent randomness in the system or heterogeneity e.g. within human populations, and epistemic, due to lack of knowledge or insufficient knowledge about the system or some part of it itself. In 2018, the European Food Safety Agency (EFSA) endorsed a new guideline addressing uncertainties which should be taken into consideration in all EFSA scientific assessments and in which as many as possible of identified sources of uncertainty should be communicated in a transparent manner. Overall, the guideline advocated for uncertainty analysis that, among other, takes both aleatory and epistemic uncertainty into consideration. One way to do this is to embed a risk assessment model in a fully Bayesian framework, characterising epistemic uncertainty in model parameters with probability distributions and opening up for propagation of uncertainty through the model. For a QMRA, the models for the different stages from contaminated meat at retail to illness need to be linked into a single model and to characterise uncertainty in parameters by a joint probability distribution.

The aim of this thesis is to evaluate an approach to perform Bayesian calibration of multiple models used in a QMRA with the purpose to quantity uncertainty in parameters and model predictions. Uncertainty in parameters is being characterised by Bayesian calibration of published models covering the different mentioned stages. This is first done on the individual models, and then jointly, but using the posterior as priors in the linked model. Bayesian calibration of multiple linked models allows for quantification of uncertainty in parameters, including those parameters linking the models together. Data for the calibration is taken from the publications used in this thesis and the Finnish public Campylobacter cases statistics which is used for a case study to evaluate the linked model alongside with an uncertainty analysis of the model. Bayesian model calibration is demonstrated as an useful approach to quantify uncertainty within an assessment model.

Populärvetenskaplig sammanfattning

Utbrott av Campylobacter håller på att bli mer återkommande speciellt under varma säsonger i Sverige. Det finns olika modeller som används i kvantitativa mikrobiologiska riskbedömning (Quantative Microbiological Risk Assessment, QMRA) av kontamination av Campylobacter vid kycklingskonsumtion och som representerar olika fas i matproduktion och konsumtion. Consumer Phase Models (CPM) används för att beräkna risken av korskontamination under hantering av kyckling som leder till en viss koncentration av bakterier vilket förtärs av en person. Koncentrationen kan därefter matas in en dos-responsmodell för att uppskatta risken att bli sjuk av Campylobacter på grund av den dosen som upptas, antingen för sig själv eller i kombination med andra faktorer.

Med kvantitativ riskbedömning får man möjligheter att behandla osäkerhet i modellen på ett explicit sätt. Osäkerheten kan delas i två olika typer: aleatorisk osäkerhet som hänger ihop med systemets inneboende slumpmässighet och epistemisk osäkerhet vilket är förknippad med begränsad eller brist av kunskap. Under 2018 godkände Europeiska byrån för livsmedelssäkerhet (EFSA) en ny vägledning för osäkerhetsanalys som bland annat uppmanar att man ska inkludera så många som möjligt identifierbara osäkerheter i en riskbedömning. Ett sätt att göra detta är att bädda in en riskbedömningsmodell i ett Bayesianskt ramverk som karakteriserar osäkerhet i modellparametrar med sannolikhetsfördelningar och som tillåter spridning av osäkerhet genom modellen. För en QMRA kräver detta att man kopplar de modeller för de olika stadier från förorenat kött i detaljhandeln till sjukdom och att osäkerhet i parametrar karakteriseras genom en gemensam sannolikhetsfördelning.

Syftet med detta arbetet är att validera en Bayesian Evidence Synthesis-modell (BES) för osäkerhetsanalys på en QMRA. Osäkerhet i parametrar kommer att karakteriseras baserat på tillgängliga data från redan publicerade modeller för prevalens och dos-respons och på tilldelade fördelningar vid behov för parametrar i CPM-modeller. Osäkerhet i parametrarna kommer spridas till osäkerhet i output för bedömning under olika riskbedömningsscenarier. BES valideras genom att karakteriseringen av epistemisk osäkerhet förblir stabil efter att modellerna kopplats, vilket är en del av en osäkerhetsanalys. Vidare genomförs ett studiefall i syfte att jämföra modellens resultat med existerande data på utbrottsintensitet för utvärdering av modellen. Både osäkerhetsanalysen och fallstudien visar att BES-modellen under en QMRA var gångbar och därmed lyckad.

Acknowledgements

I would like to express a gratitude to Ullrika Sahlin for her seemingly unwavering support throughout this project. I am truly thankful for everything I have learnt from this project under her guidance. I was introduced to the topic of this thesis by Roland Lindqvist at Swedish Food Agency and I also wish to thank him for his feedback and comments which helped to improve this thesis. Finally, I would like to thank family and friends for their support.

Thank you!

"... It's like this. Sometimes, when you've a very long street ahead of you, you think how terribly long it is and feel sure you'll never get it swept. And then you start to hurry. You work faster and faster and every time you look up there seems to be just as much left to sweep as before, and you try even harder, and you panic, and in the end you're out of breath and have to stop–and still the street stretches away in front of you. That's not the way to do it.
You must never think of the whole street at once, understand? You must only concentrate on the next step, the next breath, the next stroke of the broom, and the next, and the next. Nothing else.
That way you enjoy your work, which is important, because then you make a good job of it. And that's how it ought to be.
And all at once, before you know it, you find you've swept the whole street clean, bit by bit. What's more, you aren't out of breath. That's important, too..."

—Michael Ende, Momo

"Yes, that's true", admitted Rhyme, "but it's not just learning things that's important. It's learning what to do with what you learn and learning why you learn things at all that matters."

—Norton Juster, The Phantom Tollbooth

Contents

Abbreviations

BES Bayesian Evidence Synthesis.

CFU or cfu Colony-Forming Unit.

CPM Consumer Phase Model.

DAG Directed Acyclic Graph.

JAGS Just Another Gibbs Sampler.

MC Monte Carlo.

MCMC Markov chain Monte Carlo.

QMRA Quantitative Microbial Risk Assessment.

TPCM Temporal-Prevalence-Concentration Model.

1 Introduction

1.1 Background

Decision makers are sensitive to knowledge-based (epistemic) uncertainty and therefore it is important to evaluate the impact of uncertainty on an assessment of risk [5, 4, 15]. Quantifying uncertainty in parameters by subjective probability makes it possible to implement the assessment model in a Bayesian framework which allows the integration of multiple sources of data and quantification and propagation of uncertainty in a transparent way. Although Bayesian analysis (or inference) is increasingly being used for statistical modelling and is being applied on quantitative uncertainty analysis in risk assessment [13, 23], there is a need to demonstrate its use and to tackle challenges when implementing it on real assessment problems. Quantitative uncertainty analysis may be demanding when the ambition is to implement big and complex assessment models in a Bayesian framework, which may require computational resources. Bayesian updating can be done sequentially, e.g. when new information becomes available. An assessment model can be big because it is an integration of several sub-models. Here it can be relevant to explore the possibilities of using sequential (or partial) updating of models, one model at a time. I explore this using an example from quantitative risk assessment.

Campylobacter, a microbial pathogen, is one of the most common bacterial cause of stomach illness in Sweden [30]. Campylobacteriosis is an infectious disease caused by Campylobacter that could be found in, among others, raw chicken meat [2, 24]. Campylobacteriosis is becoming an increasing problem in Sweden and there is a need to assess the risk associated with the exposure of campylobacteriosis [7, 6, 17].

Quantitative Microbiological Risk Assessment (QMRA) of Campylobacter contamination use several models to describe the exposure and the paths from exposure to effect during different stages in food production and food consumption and there are QMRA made specifically for campylobacteriosis in Sweden [18]. Prevalence and concentration models, for short prevalence model, explain the prevalence of Campylobacter in retail meat and in what concentration they occur. To estimate the contamination of Campylobacter during consumption, for example in the kitchen, some different consumer phase models (CPM) are used. Finally, there is a dose-response model that estimates the probability of becoming infected respective falling ill with Campylobacteriosis. A practical challenge is to integrate the different models into one model and update parameters within individual models including parameters linking models together. Sometimes data can support calibration of an individual model. In other cases, such as for the CPM models, calibration is only possible when a model has been integrated with the other models, since data is related to inputs and outputs of the assessment and only partly available to inform the parameters of the individual CPMs. Linking several models together would enable a complete probabilistic uncertainty analysis and the possibility to calibrate and evaluate the assessment model, or part of the assessment model.

1.2 Aim of the Thesis

The aim of this thesis is to evaluate an approach to perform Bayesian calibration of multiple models used in a QMRA with the purpose to quantity uncertainty in parameters and model predictions.

In this study, the two models for assessment of prevalence and concentration (prevalence model) and the likelihood of being ill given a certain dose (dose-response model) for which uncertainty has been quantified in a Bayesian framework, will be integrated with two models for the transfer rate in the consumer phase (the CPM models) which, as different from the other individual models, are not supported by published quantitative characterisation of uncertainty in their parameters, partly because it is difficult to inform them from data without access to a joint model.

In order to achieve the aim, I will

1. Identify different models for a QRMA
2. Implement these models into a common framework to quantify epistemic uncertainty
3. Find a way to combine the models while preserving characterisation of epistemic uncertainty in each model
4. Perform an uncertainty analysis asking what parameters contribute the most to the uncertainty in the output of the combined model (for example the probability of becoming ill after handling raw chicken in the kitchen.)
5. Use a case study with Finish health data to compare accuracy and precision of predictions based on different CPMs.

The structure of this thesis is as follows. Section 2 brings up the theory with further details of the ideas. Section 3 explains the methods used in this thesis. Section 4 presents the result. Discussion is then followed up in Section 5. Finally, conclusions are made in Section 6.

2 Theory

2.1 Uncertainty Analysis

The purpose of uncertainty analysis is to identify and characterise uncertainty in decision relevant quantities from an assessment [4]. Epistemic uncertainty is conditional on the knowledge available at the time of the assessment. Epistemic uncertainty that are dealt with here can be attributed to the value of model parameters (which in this context are seen as fixed but uncertain) or the validity about the model itself (also called structural uncertainty) [29]. Aleatory uncertainty is an inherent attribute in a system and is naturally taken into account by stochastic and statistical modelling. The influence of sources to uncertainty can be evaluated by sensitivity analysis, which can give an indication on which parameters it is worth while to collect more knowledge to at best reduce their uncertainty.

2.2 Bayesian Analysis

A Bayesian analysis begins with expressing uncertainty in parameters within a model by probability and use probabilistic models for data (likelihood) and Bayes rule to update parameters based on new information (data) [10, 14, 27, 16, 11]. In Bayesian analysis, it is possible to integrate expert knowledge and data and to quantify uncertainty using probability. The updated uncertainty about parameters is referred to as the posterior distribution, and is a joint probability distribution over all parameters.

Bayesian analysis is useful to support probabilistic uncertainty analysis [23]. Uncertainty is quantified in any part of the model by propagating uncertainty in parameters to the quantities of interest. Care must be taken to ensure the assessment model includes the relevant parts of aleatory uncertainty [13], and that, when needed, epistemic uncertainty is distinguished from aleatory uncertainty when propagating.

2.3 Bayesian updating using MCMC sampling

Bayesian updating can be obtained by sampling from the posterior. More specifically, a sampling or a simulation during which the posterior (or any distribution) is being sampled extremely many times is called Monte Carlo simulation. Together with Markov chain, which is a random walk where each step is independent of the previous step, the simulation becomes a process called Markov chain Monte Carlo, MCMC. A MCMC process makes it possible to sample from complicated distributions or models, while ensuring convergence in the models. There are several different versions of MCMC sampling and one of them is so called Gibbs sampling [14].

The procedure of Gibbs sampling is as follows: at each step in the walk, one of the parameters is selected and then be compared to a new value drawn from the conditional probability distribution, conditioning on the rest of the parameters and data. This process is repeated cycledly through all the parameters many times.

For example, call the parameters, or component parameters, θ_1, θ_2, θ_3..., and for a selected parameter θ_i, a value is drawn from its conditional probability, $P(\theta_i|\theta_{j\neq i}, D)$, where D is the data. Then we get the new position or step consisting of the new value θ_i along with the other unaltered values $\theta_{j\neq i}$. Now we repeat this with another selected parameter and draw from its

corresponding conditional probability given the new value of θ_i. This is repeated while cycling through all the parameters θ_1, θ_2, θ_3... many times, creating a long chain.

BUGS and JAGS are two software built for Gibbs sampling (which is an example of MCMC sampling) [25, 20]. BUGS and JAGS use the graphical representation of a Bayesian model, which means the code consists of nodes for variables and parameters and marginal or conditional probability distributions over these. There are other software for MCMC sampling but these two are mentioned here as these were used in the published studies.

2.4 Bayesian model calibration

An assessment model is in a sense a computer model specified to approximate the system under study. Model calibration is the process of learning about unknown parameters of a computer model by fitting model predictions to physical observations of the system, which can be done in a Bayesian framework (Kennedy and O'Hagan 2001). Bayesian model calibration has the advantage of allowing for prior specification of parameters and results in uncertainty in parameters quantified by probability.

Bayesian Evidence Synthesis (BES) is a term used when Bayesian model calibration consider multiple sources of evidence on parameters that are shared between statistical models for data/evidence and the assessment model. Bayesian model calibration and BES are ideal for informing assessment models by providing a framework to integrate different sources of evidence, e.g directly and indirectly relevant data or information, and propagate the uncertainty through an assessment model to the assessment outputs [1, 12, 29].

The Bayesian framework allows for one-step simulation, i.e. a single analysis where the resulting posterior distribution (output from data analysis) could be feed directly into another model without using an "intermediate summary step" [29]. In this way, the analysis derives the joint posterior distribution of all unknown parameters from a Bayesian probability model and run both evidence synthesis and the linked models simultaneously. In this integrated approach, the resulting uncertainty is propagated through the predictive model. Since the evidence from the data has to be propagated backwards to update the parameters, or to propagate the uncertainty backwards, and then forwards through the linked models, MCMC is needed (rather than only Monte Carlo method).

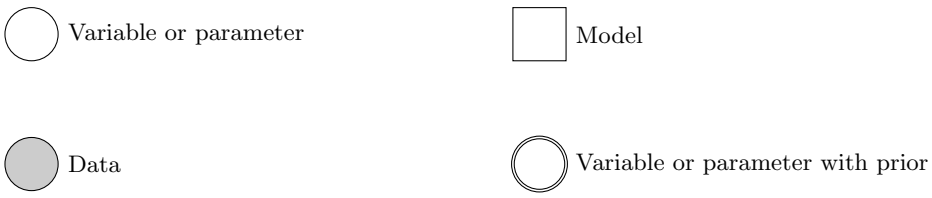
This is in contrast to the two-stage process, i.e. carrying out the parameter estimation in one step and then feeding the resulting summary of the joint posterior distribution into the separate probabilistic sensitivity analysis (of the second model) [29].

Advantages of Bayesian model calibration are as follows:

- It is not necessary to make any assumption about "parametric distributional shapes for the posterior probability distributions". Also, sometimes closed-form expectations may not exists.
- Instead of making assumptions about the dependence/independence between different quantities, the probabilistic dependencies between parameters are being propagated in the analysis.
- It is possible to continue to update the model when new data are available.

2.5 Directed acyclic graphs

Bayesian models (including an assessment model embedded in probabilistic uncertainty analysis) are probabilistic graphical models that are specified from directed acyclic graphs, DAGs. Quantities at the start of an arrow in the graph give rise to the quantities at the end of the arrow. They are called parents respective children. The quantities are also called nodes and in this study we are going to use four different kinds of nodes:



2.6 QMRA models

2.6.1 Overview of the QMRA models

Four models have been identified and selected for the QMRA. One model is for contamination of Campylobacter in retail meat, two consumer phases models and one dose-response model. What follows is a short description of the selected models covering different stages:

- Contamination of retail meat: prevalence and concentration model, which estimates the prevalence and concentration of Campylobacter in retail meat
- From retail meat to human exposure: consumer phase model, CPM, which describes the contamination of food during preparation and handling of raw chicken meat in kitchen. The output of this model is the amount of ingested Campylobacter
- From human exposure to health effect: dose-response model which estimates the probability of becoming infected or ill after consuming the contaminated meat (i.e. a given amount of Campylobacter)

In the following sections, all the different models will be individually presented in detail, including the different CPMs.

2.6.2 Prevalence and Concentration Model

The model by Mikkela et al [21] is used as the prevalence and concentration model (prevalence model in short). The objective of the particular prevalence model was to estimate prevalence and concentration in retail meat using Bayesian methods while the data is censored and clustered.

Their study was done on Campylobacter concentration sample data obtained from grocery stores and from different months in the Helsinki area, Finland. The Helsinki area represents the whole country, since the companies deliver the poultry meat all over Finland. Moreover, those companies cover over 90 % of the total production in Finland.

The meat samples are of two types, chicken meat respective turkey meat. Furthermore, several samples could be taken from one same food batch (hence clustered data) and the number of one sample varies, as well as does the size of one batch.

The model predicts seasonal prevalence (% for each month) and concentration of Campylobacter (cfu/g) in retail meat, for both chicken meat and turkey meat.

The detection and quantitative data was used separately in the model. With the detection data, the percentage of contaminated retail foods or prevalence (pf) could be estimated. This was done by estimating the prevalence within food batches respective (seasonal) prevalence between food batches. The percentage, pf, is a product of the these two different kinds of prevalence: within-batches prevalence, pw, and seasonal between-batches prevalence, pb_m. Since the between-batch prevalence is seasonal, it is modelled as a Markovian time serie:

$$Logit(pb_m) = Logit(pb_{m-1}) + e_m, \quad m = 2, ..., 12, \tag{1}$$

where the parameter e_m represents the changes between consecutive months. The within-batch prevalence is not seasonal, due to insufficient data.

In their study, they used two different hierarchical models for concentration estimation based on the quantitative data (enumeration data), of which only one will be used in this study. The hierarchical log-normal model was better supported by data (both chicken and turkey) than the alternative model (hierarchical gamma model), and is hence chosen to be included in this study.

In detection and quantitative determination of Campylobacter in meat samples, the positive concentrations that are below 0.5 cfu/g were not being quantified, due to the "limit of determination of the microbiological methods". So these data was treated as censored data, so called left-censored (`NA` in the data). In the study, the data set contains a high amount of censored data. Furthermore, it is assumed that the minimum concentration for positive samples was 1 cfu/ws, where ws denotes the weight of one test portion which is 25 gram. This resulted in a censored interval between 0.04 ($= \frac{1}{25}$) cfu/g and 0.5 cfu/g. This assumption was kept intact in this study.

The fully detailed model of the prevalence model, including priors on different parameters, is simply presented as a directed acyclic graph, DAG (Figure 1). The prevalence has been published with code in OpenBUGS [21].

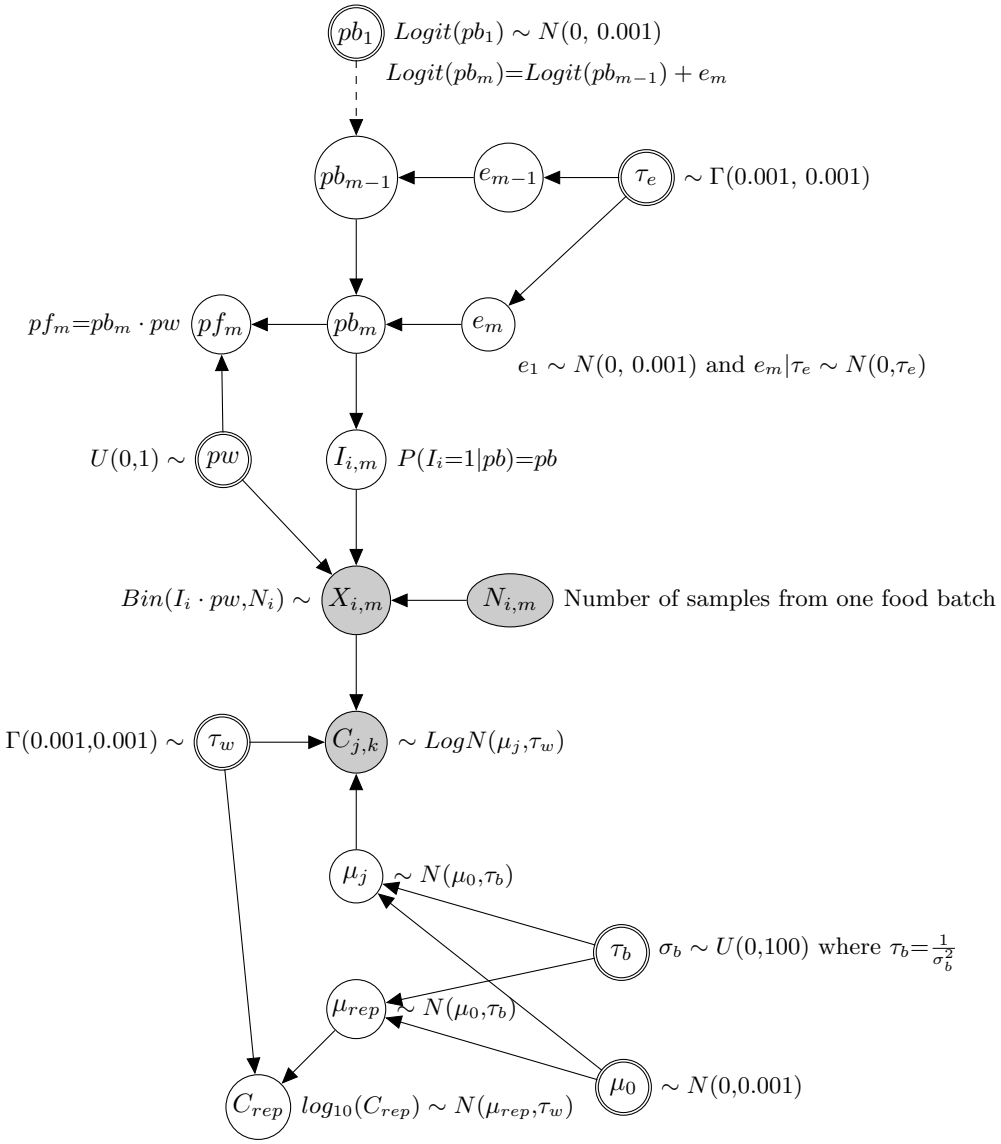


Figure 1: The prevalence model estimates both prevalence, pf_m, and predicted concentration, C_{rep}. e_m represents changes between consecutive months. The indicator $I_{i,m}$, which is a binary latent variable, describes the "true" contamination status of a batch and is either 1 if at least one of the units in a batch i is contaminated, and is 0 otherwise, with $P(I_i = 1|\text{pb}) = \text{pb}$. $c_{j,k}$ is the quantitative data (enumeration data). $\mu_0 \sim U(0, 100)$ means that μ_0 is sampled from $U(0, 100)$.
Indices: $m = 2, ..., 12$; $i = 1, ..., B$ where B is the total number of studied batches per meat type; $j = 1, ..., J$ where J is the number of detected contaminated batches and $k = 1, ..., t_j$ where t_j is the number of detected contaminated samples in a batch j.

2.6.3 Consumer Phase Models

A Consumer Phase Model (CPM) covers the part of the food chain between buying at retail and exposure, when the consumer purchased, transports, stores, prepares and finally consumes the retail food. It is the part where authorities or professionals often aren't able to control, and the only possibility for control is via education and other information provision for the consumers.

Nauta et al. [22] has conducted a study where they compare several existing CPMs for Campylobacter in chicken meat. These CPMs describe various cross-contamination during preparation of the raw meat, by identifying different transfers in kitchen, for example from a cutting board to salad. Eight CPMs, from different studies, were included in their study. Finally, they put the dose output of these CPMs into a dose-response model for the final comparison. Their objective was to study the different CPMs and their impact on QMRA (quantitative microbiological risk assessment, see Section 2.6.1), by using different scenarios and comparing the predicted relative risk reductions.

In this study we adopted two out of the eight CPMs, which is described in the two next sections. Uncertainty in parameters of the CPMs is being expressed by probability distributions. The choice of distribution is here based on data from Luber et al. [19]. The data on some of the transfer rates, which will be described in the next following sections, was collected by Luber et al. [19] and which will also be used to calibrate the parameters for the transfer rates. The CPM models are then linked with a dose-response model as well (Figure 2). Here their dose-response model was excluded since another model (Section 2.6.6) is chosen to be used here. In the article by Nauta et al. [22], it was assumed that portion sizes of consumed meat, w_c, are distributed as a lognormal distribution with mean 189 gram and a standard deviation of 127 gram, with maximum of 1000 g. The assumption is retained in this study.

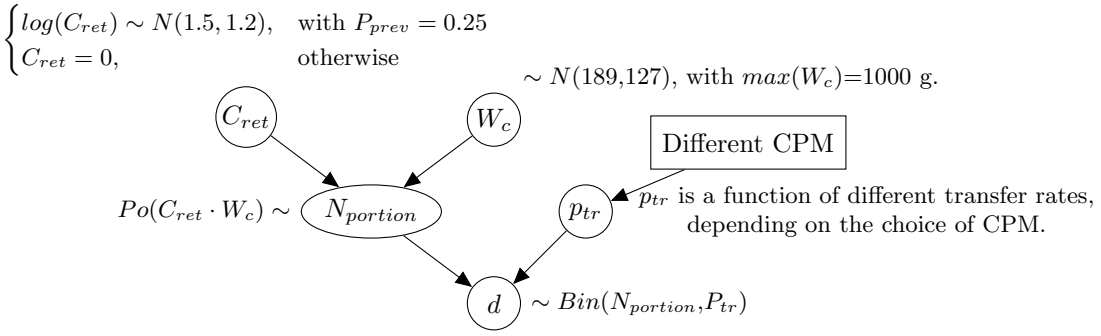


Figure 2: The model with CPM used by nauta et al. [22]. $N_{portion}$ is the number of Campylobacter on one portion of chicken meat (cfu) and C_{rep} is the Campylobacter concentration in retail meat. W_c represents portion sizes, for example the mean is 189 g. P_{pr} is a function of different transfer rates and other variables describing the cross-contamination, depending on choice of CPM. It describes the probability of a single cfu from the portion to end up in the consumed or ingested dose, d.

2.6.4 Christensen CPM

We follow the approach by Nauta et al. and use a simplified version of the CPM by Christensen et al. [22]. The probability of a single cfu from the portion to end up in the dose, p_{tr}, is as follows:

$$p_{tr} = t_{CE}(t_{EC} \times f_{CC} + (1 - t_{EC} \times f_{CC}) \times t_{ES} \times f_{CS}), \tag{2}$$

with the transfer rates as described in Table 1 and Table 2.

	Chicken, C	Equipment, E	Salad, S
Chicken, C	f_{CC}	t_{CE}	f_{CS}
Equipment, E	t_{EC}	-	t_{ES}
Salad, S	-	-	-

Table 1: The transition matrix illustrates the contamination of Campylobacter in kitchen, using Christensen CPM model. For example, t_{CE} is the transfer rate of Campylobacter from raw chicken to equipment (board or knife) in kitchen and f_{CC} is the frequency of contamination from a piece of chicken to another piece.

Parameter	Explanation	Prior	Data
t_{CE}	transfer rate raw chicken to equipment	$Beta$	Luber et al.
t_{EC}	transfer rate equipment to cooked chicken	$Beta$	-
f_{CC}	frequency of chicken to chicken contamination	=1	-
t_{ES}	transfer rate equipment to salad	$Beta$	Luber et al.
f_{CS}	frequency of chicken to salad contamination	=1	-

Table 2: Prior and whether there is data for each of the parameters. The frequencies are set to one and all the transfer rates have a Beta distribution as prior. The data used here came from a study by Luber et al. [19].

The choice of prior distributions for the transfer rates are altered and simplified here, compared to the ones used by Nauta et al. [22] and the hyperparameters are transformed due to practical reasons:

$$\begin{aligned} t_{CE} &\sim Beta(t.t_{CE} \cdot s.t_{CE}, (1 - t.t_{CE}) \cdot s.t_{CE}) \\ t_{EC} &\sim Beta(t.t_{EC} \cdot s.t_{EC}, (1 - t.t_{EC}) \cdot s.t_{EC}) \\ t_{ES} &\sim Beta(t.t_{ES} \cdot s.t_{ES}, (1 - t.t_{ES}) \cdot s.t_{ES}) \end{aligned} \tag{3}$$

The hyperpriors for the transformed hyperparameters are described in Table 3.

Hyperparameter	Hyperprior
$t.t_{CE}$	$Beta(1,1)$
$t.t_{EC}$	$Beta(1,1)$
$t.t_{ES}$	$Beta(1,1)$
$s.t_{CE}$	$Gamma(1,1)$
$s.t_{EC}$	$Gamma(1,1)$
$s.t_{ES}$	$Gamma(1,1)$

Table 3: Hyperpriors for the transformed hyperparameters in the Christensen CPM.

2.6.5 Mylius CPM

The Mylius CPM is another CPM used by Nauta et al [22]. The model includes washing as a part of cross-contamination. The probability, p_{tr}, is as follows:

$$p_{tr} = (t_{C,H} \times t_{H,H} \times t_{H,S} + t_{C,B} \times t_{B,B} \times t_{B,S}) \times t_{S,S}, \tag{4}$$

with the transfer rates as described in Table 4 and Table 5.

	Chicken, C	Board, B	Hand, H	Salad, S
Chicken, C	-	t_{CB}	t_{CH}	-
Board, B	-	t_{BB}	-	t_{BS}
Hand, H	-	-	t_{HH}	t_{HS}
Salad, S	-	-	-	t_{SS}

Table 4: The transition matrix illustrates the contamination of Campylobacter in kitchen, using Mylius CPM model. For example, t_{CB} is the transfer rate of Campylobacter from chicken to board and t_{BB} is the persistence after hand washing.

Parameter	Explanation	Prior	Data
$t_{C,H}$	Transfer rate chicken to hand	$Beta$	Luber et al.
$t_{H,S}$	Transfer rate hand to salad	$10^{-Normal(1.90,0.606)}$	-
$t_{C,B}$	Transfer rate chicken to board	$Beta$	Luber et al.
$t_{B,S}$	Transfer rate board to salad	$10^{-Normal}$	Luber et al.
$t_{H,H}$	The persistence after hand washing:		
	1. no washing (20%)	=1	-
	2. washing (80 %)	$Beta(0.24, 6.67)$	-
$t_{B,B}$	The persistence after board washing:		
	1. other side of board (33 %)	=0	-
	2. same board, no washing (5%)	=1	-
	3. washing (62%)	$Beta(0.25, 400)$	-
$t_{S,S}$	The persistence after salad washing:		
	1. no salad washing (40%)	=1	-
	2. salad washing (60%)	$Beta(3.25, 4.7)$	-

Table 5: Prior and whether there is data for each of the parameters. Some of the parameters have different persistence depending on the case. For example the persistence of Campylobacter after hand washing, $t_{H,H}$, is 100 % if there was no washing, which occurs to 20 % of the meals. Otherwise, the persistence follows a Beta distribution. The data from a study by Luber et al. [19] was used here.

Similarly, the prior distributions are altered and the hyperparameters are transformed as given in Equation (8) and hyperpriors are described in Table 6.

$$\begin{aligned} t_{C,H} &\sim Beta(t.t_{CH} \cdot s.t_{CH}, (1 - t.t_{C,H}) \cdot s.t_{CH}) \\ t_{C,B} &\sim Beta(t.t_{CB} \cdot s.t_{CB}, (1 - t.t_{C,B}) \cdot s.t_{CB}) \\ t_{B,S} &\sim 10^{-Normal(\mu_{t_{BS}}, \tau_{t_{BS}})} \end{aligned} \tag{5}$$

Hyperparameter	Hyperprior
$t.t_{CH}$	$Beta(1, 1)$
$t.t_{CB}$	$Beta(1, 1)$
$\mu_{t_{BS}}$	$Normal(0, 1)$
$s.t_{CH}$	$Gamma(1, 1)$
$s.t_{CB}$	$Gamma(1, 1)$
$\tau_{t_{BS}}$	$Gamma(1, 1)$

Table 6: Hyperpriors for the transformed hyperparameters in the Mylius CPM.

2.6.6 Dose-Response Model

In QMRA (see Section 2.6.1), a dose-response model is included to estimate the response (i.e. becoming infected or ill) given an amount dose of Campylobacter. For this study, we use the

dose-response model from Teunis et al. [31].

The dose-response model used by Teunis et al. [31] is conducted as a meta-analysis, using multilevel model. They categorize data from several studies into three different host species groups: controlled human infection model, i.e challenge experiments with human; outbreaks involving contaminated raw milk; and challenge studies in non-human primates.

Furthermore, strain varies from one study to another study and in total there are eight different strains, including unidentified outbreak strains. Overall, the data consists of host species, strain, ingested dose, number of exposed, number of infected (i.e. shedding or seroconverting) and numbers with symptoms (i.e. symptoms of acute campylobacteriosis).

One of the objectives with the study by Teunis et al. [31] was to study the variation in dose-response with strain and host effect. They did this by comparing different dose-response models based on different strain and host. They also made a comparison of infectivity and pathogenicity (which is represented as two parameters in their models) across the different strain and host. It was shown that for infection, the hosts do not have different effects. As for illness, it was observed that there are difference between human/primates and outbreak (i.e. the pathogenicity parameter is shown to be higher for all outbreaks than for the human/primate challenges, that results in a steeper curve).

In this study, we are going to use the dose-response model for infection (Figure 3), which is the same for all host species, and two different dose-response models for illness (Figure 4), which represents human challenge respective outbreak. The dose-response model has been published with code in JAGS along with its data. For more details of the model, see the reference [31].

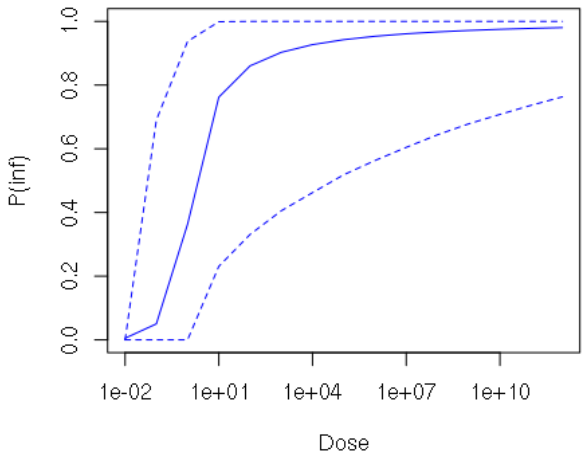


Figure 3: The infection dose-response model with 95% posterior credible interval by Teunis et al. [31]. The curve shows the relationship between the ingested campylobacter dose (logit-transformed scale) and the likelihood of becoming infected. The curve is the same for both human challenge and outbreak.

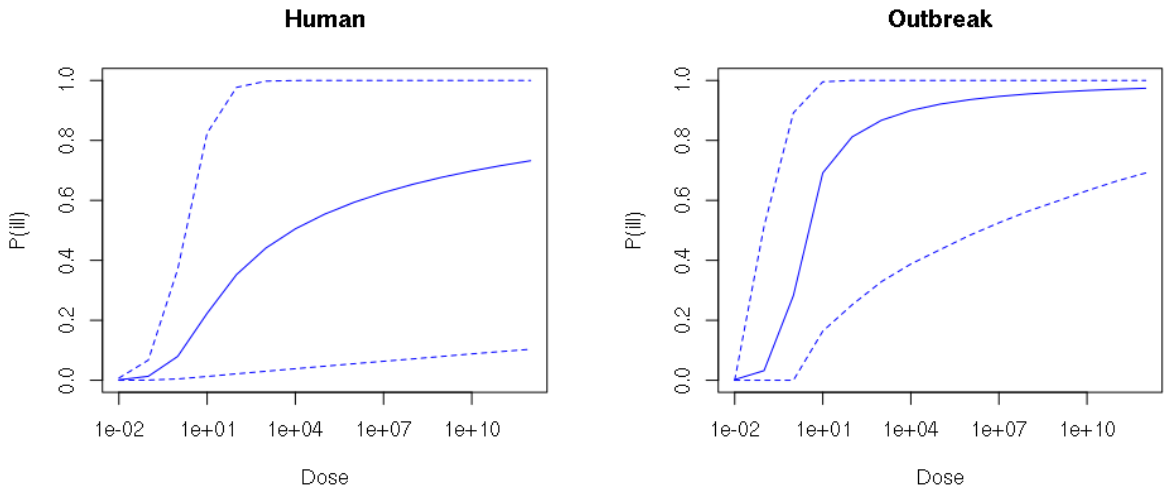


Figure 4: The illness dose-response models with 95% posterior credible interval by Teunis et al. [31]. The curves shows the relationship between the ingested campylobacter dose (logit-transformed scale) and the likelihood of becoming ill, i.e. acute campylobacteriosis. They were modelled with the data from human challenge (left) respective outbreaks (right).

3 Method

The first step is to build a modelling environment which successfully reproduce the identified models and data for QMRA. The second step is to verify the models are reproduced even after they have been combined. The third step is to perform a probabilistic uncertainty analysis, use a case study to quantify uncertainty in relevant output variables and use sensitivity analysis to analyze whether there are parameters which give largest contribution to uncertainty of the output variables and to identify them. Since this study integrates different kind of data from different sources and uses priors based on earlier information, Bayesian evidence synthesis is suitable to be the approach for uncertainty analysis.

3.1 Reproduction and combination of models

Two of the assessment models were implemented with MCMC sampling, one in JAGS and the other in BUGS. Here, JAGs was chosen for the combined model. Reproduction of individual models were done to by implementing them in JAGS, and verify the code by running them with original priors and compare results those in the corresponding publications. In practice, it means reproduction of existing code of the individual models and to make sure that the code works, i.e. for example that the values of parameters are in accordance with the existing result and to check whether the MCMC chains converge.

First, it is noted that both the prevalence model and the dose-response model are already well-adjusted, based on data used by Mikkelä et al. [21] respective Teunis et al [31]. To avoid the possibility of (high) uncertainty to be propagated from consumer phase model, CPM, to the prevalence and dose-response models, we restraint the possibility by using informed priors for the parameters in prevalence and dose-response parts in the combined model. The informed priors are based on the posterior from the individual models, i.e. from when the models are run individually and then fitted to a distribution in R (i.e. calibration of the individual models).

The next step is to combine the models into a model for the contamination during the whole process from retail to consumption and the risk of becoming ill after consuming contaminated meat. The combined model would also make predictions about campylobacteriosis. The combined model (Figure 5) consisted of the prevalence model used by Mikkelä et al. [21], two CPMs used by Nauta et al. [22] and the dose-response model used by Teunis et al. [31]. In this study, the two chosen CPMs are named Christensen CPM and Mylius CPM. This combination resulted in two different combined models.

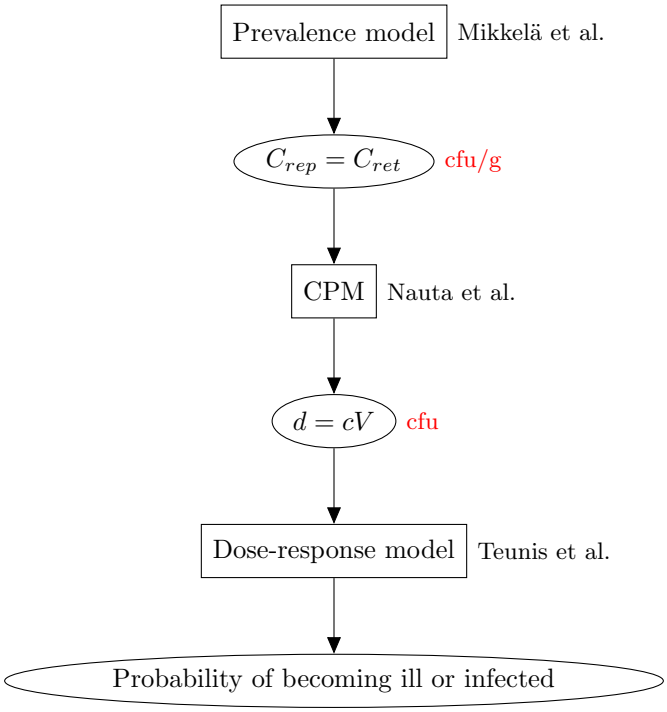


Figure 5: The combined model consists of the the prevalence model used by Mikkelä et al. [21], two CPMs used by Nauta et al. [22] and the dose-response model used by Teunis et al.[31] (represented as rectangles). The models are linked by the output/input variables C_{rep}/C_{ret} and d/cV (ellipses).

The purpose of the combined model was primarily to do joint sampling from all models in a one-step approach (see BES). To ensure parameters in each model stayed close to the posterior when running them individually, informed priors were used in the combined model. The informed priors were in general derived by fitting distributions to marginal posterior, and sometimes other solutions were sought (see results).

The reproducibility of the individual models was checked when run with informed priors first individually and then the combined models was run along with the updated informed prior (i.e. the marginal posterior from the individual models). This was done by, for a set of relevant parameters, comparing with the obtained marginal posteriors from the individual model respective the combined model, to the original priors respective informed priors.

The suggested approach to compare the posterior of parameters in the combined model to corresponding posterior of the individual models is a simple way to verify that the combined model is valid, i.e. that the model produce similar results as in the individual models.

3.2 Case-study

The purpose of the case-study was to have a realistic situation for which the QMRA could be evaluated against. Monthly data on campylobacteriosis cases were downloaded from the

website of the Finnish National Institute for Health and Welfare [9]. This data covers whole Finland, as the prevalence model is calibrated with data that comes from detecting and measuring concentration of Campylobacter in the poultry meat, of which companies are responsible for over 90 % of the total Finnish production. Both the Finnish campylobacteriosis data and the data used in the prevalence model by Mikkelä et al. [21] cover same time period, years 2012-2014.

3.3 Sensitivity analysis

In order to study the impact of some sources of uncertainty on the assessment output, sensitivity analysis can be seen as a part of uncertainty analysis.

To perform a global sensitivity analysis, we use the variance-based sensitivity analysis, which uses decomposed variances due to main effects, two-way interactions, and so on. Sensitivity in output to a specific input is summarised by two global sensitivity indices, or Sobols' indices. The first order index is the ratios between the variance due to the input's main effect and overall variance of the model. This tell us how sensitive the output is when varying one parameter alone. The total index is the ratio between variance explained by all types of interactions with the input and all other inputs and the overall variance of the model. This informs us how the model is affected by all its variables and their interactions. These indices corresponds to the ANOVA decomposition for linear models [28, 26]. Sensitivity analysis was done using the R-package `BASS`, which fits a response surface on a sample from inputs and corresponding model output values, before decomposing the variances [3, 8].

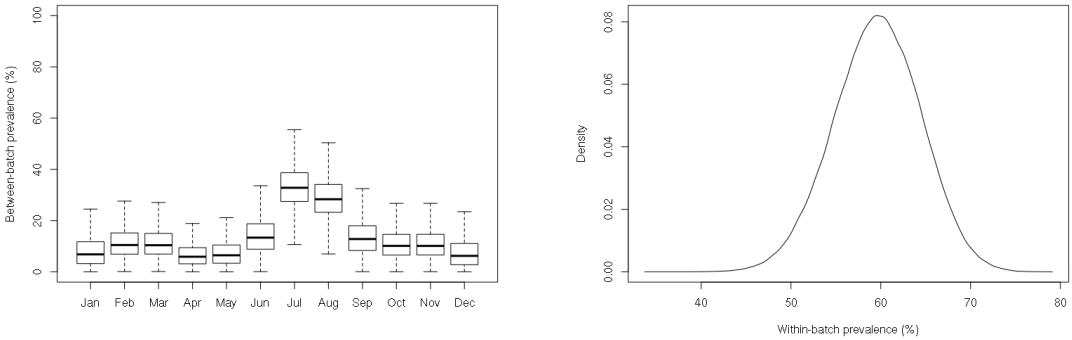
4 Results

4.1 Reproducibility of individual models

The prevalence model was given in OpenBUGS, so a BUGS-JAGS conversion of this model was needed. An issue during the conversion was that BUGS respective JAGS treats censored data in different ways. In BUGS, the function `I()` does not distinguish between truncation and censoring. However, in JAGS there are `T()` for truncation respective `dinterval()` for censoring.

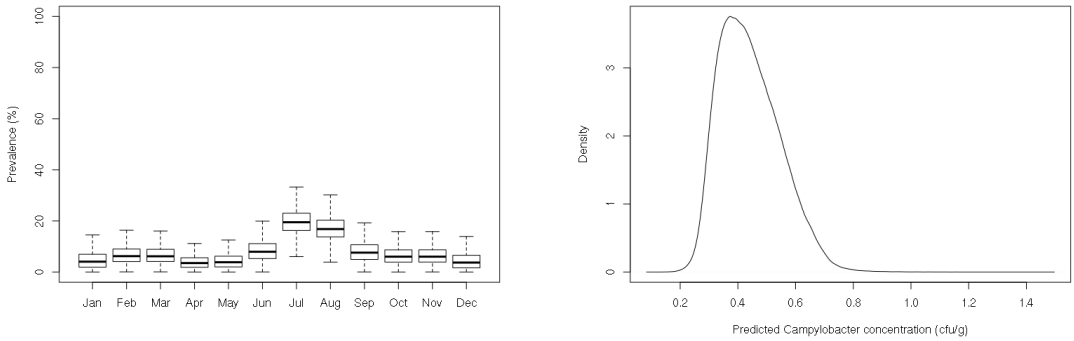
Another issue with the prevalence model was that some of the reproduced result (in JAGS) was at first not in accordance with the result given in the article by Mikkelä et al. [21]. After having been in touch with the authors, it was realized that the identical result was produced if the turkey part was removed from the code. This is believed to be due to some computational issues related to time series in JAGS and wasn't further investigated.

The prevalence model was reproduced in JAGS and the estimation of the between-batch prevalence and the within-batch prevalence were in accordance with the result by Mikkela et al. (Figure 6). Similarly, the seasonal prevalence and predicted concentration of Campylobacter were reproduced in JAGS (Figure 7).



(a) Between-batch prevalence, pb_m **(b)** Within-batch prevalence, pw

Figure 6: The reproduction of the prevalence model. Seasonal prevalence between food batches, pb_m, and prevalence within food batches, pw, of retail chicken meat.



(a) Prevalence, pf **(b)** Predicted concentration, C_{rep}

Figure 7: The reproduction of the prevalence model. Seasonal overall prevalence and predicted concentration of Campylobacter (cfu/g) in retail chicken meat. The seasonal overall prevalence is the product of the seasonal between-batch prevalence, pb_m, and the within-batch prevalence, pw.

The two chosen CPMs (Christensen CPM and Mylius CPM) were written in JAGS according to the model given in the article by Nauta et al. [22] with some changes in the distributions of the parameters for convenient reasons (for example the distribution based on Pert distribution were changed to some suitable Beta distribution, see Equation 2.6.4 and Table 10).

Some of the reproduced results for the dose-response model by Teunis et al. are not entirely consistent with the ones in their published article [31] (Appendix A). The given code, which was provided in their article, was here slightly adjusted to get the same graphs dose-response curves in their article (see Figures 3 and 4). The last code line in their code, that estimates the likelihood function of becoming ill, contains an unnecessary iteration. When removing the iteration, their dose-response graphs became reproducible.

After making the above adjustments, all the individual models were successfully run in JAGS with convergence in MCMC in all the individual models. The results of the models are reproduced and some of the results are used in this report, as a part of the description of the models (for example, see Figures 3 4, 6 and 7). Finally, the result from calibrating each individual models are later used as informed priors for the parameters in the combined model (Appendix B).

4.2 Reproducibility in the Combined Model

One of the purpose with this study is to find a way to combine the models. The resulted model would explain contamination all the way from retail to consumption and to what degree Campylobacter would cause infection respective illness.

To validate the combined model using informed priors on parameters in the prevalence and dose-response parts, the posterior of parameters in the combined models will be compared to the posterior of parameters in the individual models. Since the different individual models were combined into one model, it might be more clear to call these individual models submodels when

talking about the combined models. The submodels were linked accordingly to the description provided in Figure 5.

Upon comparing the respective posteriors of the combined models (both the model with Christensen CPM respective Mylius CPM) and the submodels with informed priors, they follow the same distribution (Appendix C). Posteriors of the parameters for the original submodels, i.e. with non-informed priors, were also added to the plots for an illustration of the difference between distributions of parameters in the model with informed priors respective non-informed priors. With the plots it was shown that the combined model is valid in the sense that it produces similar results as the submodels individually.

4.3 Uncertainty analysis of the combined models

The uncertainty analysis consists of three parts. Firstly, a quantification of uncertainty of the outputs of the combined models was made to get a picture of the uncertainty. This was done with five chosen outputs reflecting the performance of the combined model. Secondly, a case study with Finnish health data was carried out to compare accuracy and precision of the predictions using the combined models. Here the predictions will be compared with the Finnish data. Finally, a sensitivity analysis is performed in order to study the impact of parameters on the uncertainty in the output of the combined models.

4.3.1 Quantification of uncertainty in output

As a part of the uncertainty analysis, the quantification of uncertainty in different outputs (or inputs) of the combined models in different stages are investigated. The outputs from the combined models are chosen to be the prevalence from the prevalence submodel; the predicted dose from the CPMs; and the predicted probabilities of becoming infected and the predicted probabilities of becoming ill (campylobacteriosis) associated with human challenge and outbreak, see Teunis et al. [31] for more details.

In this uncertainty analysis, 200 cases or persons per month were simulated and the monthly mean of the 200 predicted doses is used (which is named Predicted mean dose in Figure 8). Likewise, the monthly predicted probabilities are actually the mean over the 200 corresponding predicted probabilities per month.

While comparing the combined Christensen model with the combined Mylius model, the uncertainty (upper 95 % limit) in the monthly mean predicted prevalences are the same (Figures 8 and 9). The uncertainty in the monthly mean predicted doses from the two combined models differ by a hundredfold (the red right axes in Figures 8 and 9). Furthermore, there are wider uncertainty intervals in the combined Christensen model compared to the combined Mylius model regarding the likelihood of of infection and the predicted probabilities of illness under both human challenge and outbreak.

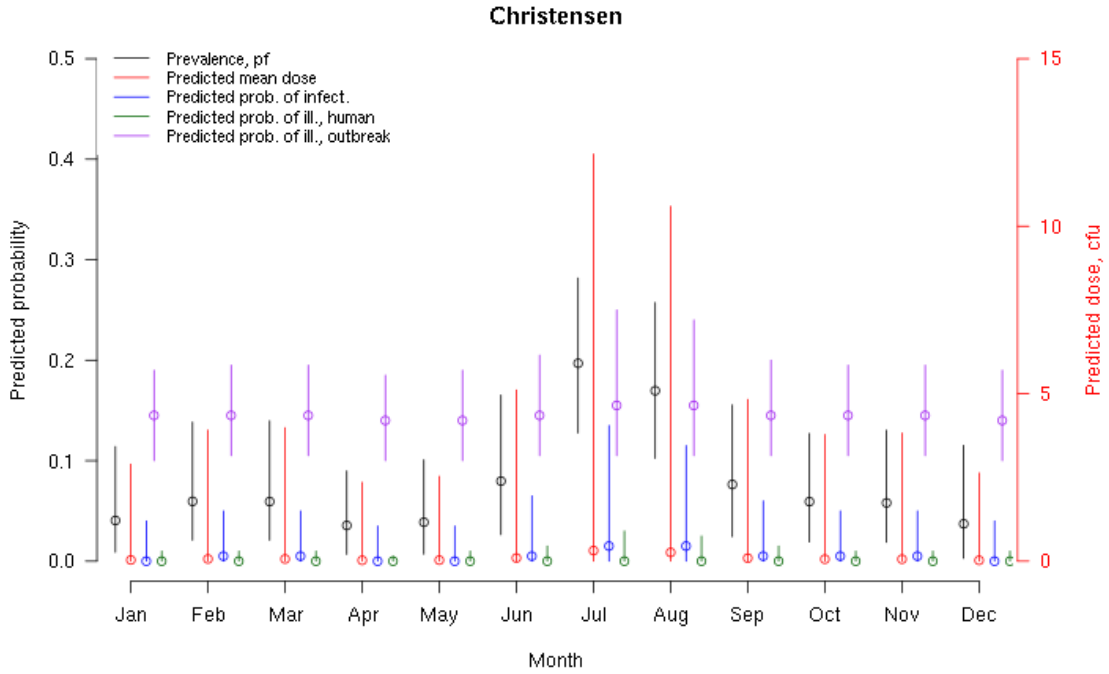


Figure 8: Quantification of uncertainty in the outputs of the combined model with Christensen CPM for every month. The predicted mean dose is on the right axis (red line). The rest is on the left axis. The predicted mean dose is the mean over 200 predicted dose under the simulation of 200 persons each month. Likewise, Likelihood of of infect is the mean over 200 predicted probabilities per month (blue line). As for the likelihood of becoming ill, there are two different predictions: one is based on the data collected from human challenges (green line) and the other is based on the outbreak data (purple line). The seasonal overall prevalence of Campylobacter is also added to the plot (black line).

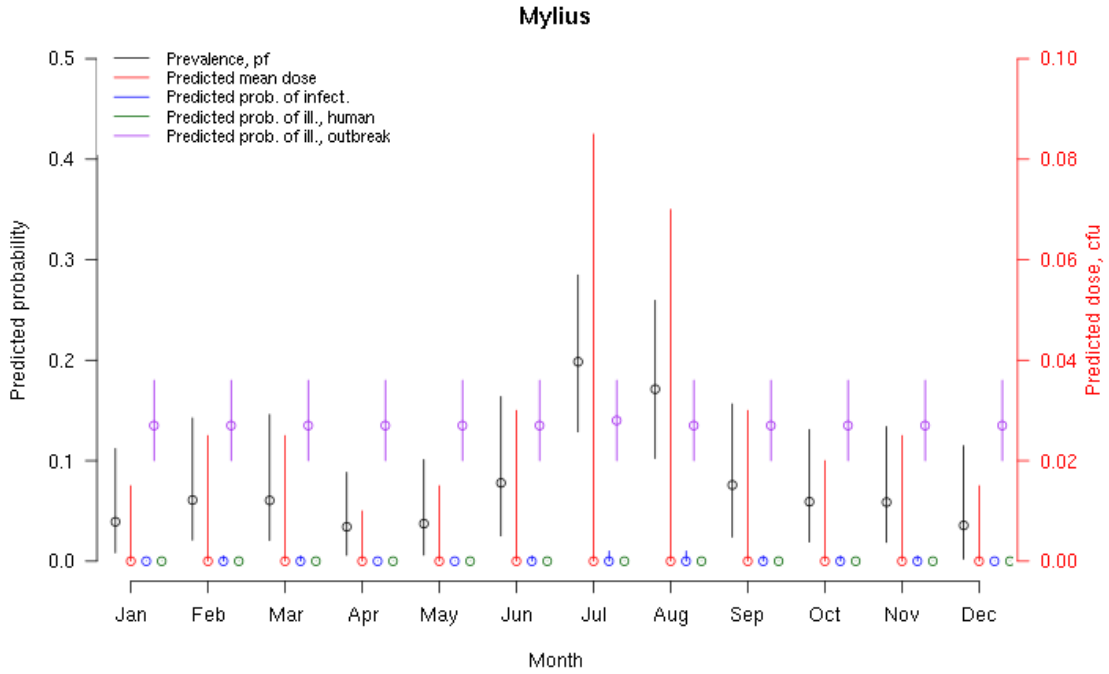


Figure 9: Quantification of uncertainty in the outputs of the combined model with Mylius CPM for every month. The predicted mean dose is on the right axis (red line). The rest is on the left axis. The predicted mean dose is the mean over 200 predicted dose under the simulation of 200 persons each month. Likewise, Likelihood of of infect is the mean over 200 predicted probabilities per month (blue line). As for the likelihood of becoming ill, there are two different predictions: one is based on the data collected from human challenges (green line) and the other is based on the outbreak data (purple line). The seasonal overall prevalence of Campylobacter is also added to the plot (black line).

4.3.2 The case study on Finnish campylobacteriosis Data

To evaluate how well the two combined models (one with Christensen CPM and one with Mylius CPM) behave compared to reality, the Finnish campylobacteriosis data will serve as a case study. To be able to make predictions about the trend of reported campylobacteriosis cases (i.e. the monthly trend of people become ill and report) using the posterior distributions of probability of becoming ill after eating chicken, the number of how many times the Finnish people eat chicken needs to be known. Since this number or data of how many times Finnish people eat chicken is unknown, we estimate this number under the assumption that the number is a constant, i.e. it doesn't depend on time (year or month) nor on CPM.

The number of how many times Finnish people eat chicken could be calibrated with the Finnish campylobacteriosis data combined with the posterior probability of becoming ill (campylobacteriosis) after eating chicken, which is the outputs from the two combined models. Note that

instead of fitting the posterior probability to a distribution, the sampled values from the MCMC chains (from the two combined models respectively) are being used as the input data alongside with the Finnish campylobacteriosis data from years 2012-2014 (Figure 10).

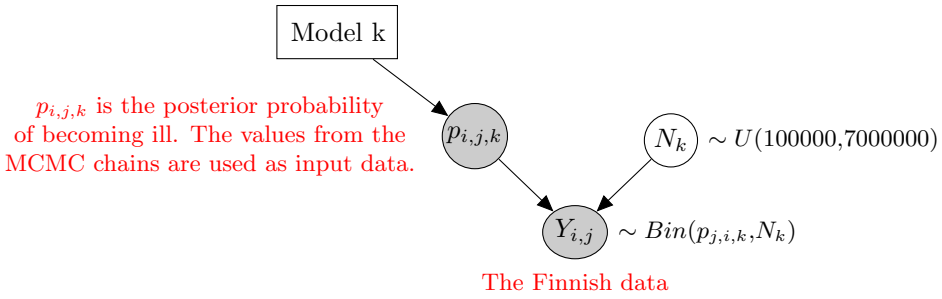
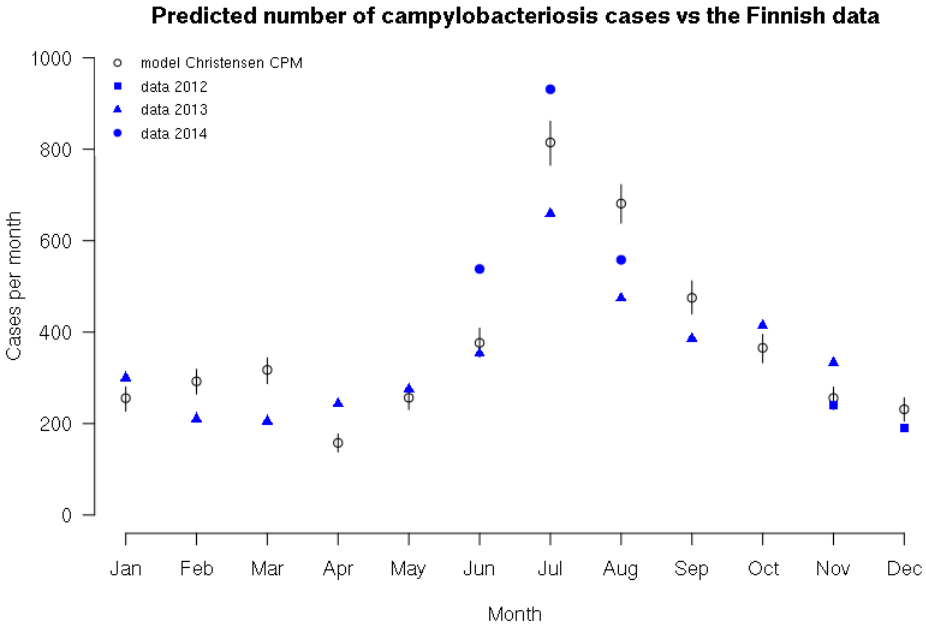


Figure 10: With the Finnish data, $Y_{i,j}$, the number of how many times Finnish people eat chicken could be calibrated, given the posterior probability of becoming ill after eating chicken calibrated for CPM model k, N_k (only for human, i.e. outbreaks are ignored). Instead of fitting the posterior, $p_{i,j,k}$, to a distribution, the 1000 values from the MCMC sampling are used as the input data. i=1, ..., 1000 (MCMC-values), j = 1,..., 12 (month) and k = 1, 2 (Christensen CPM respective Mylius CPM).

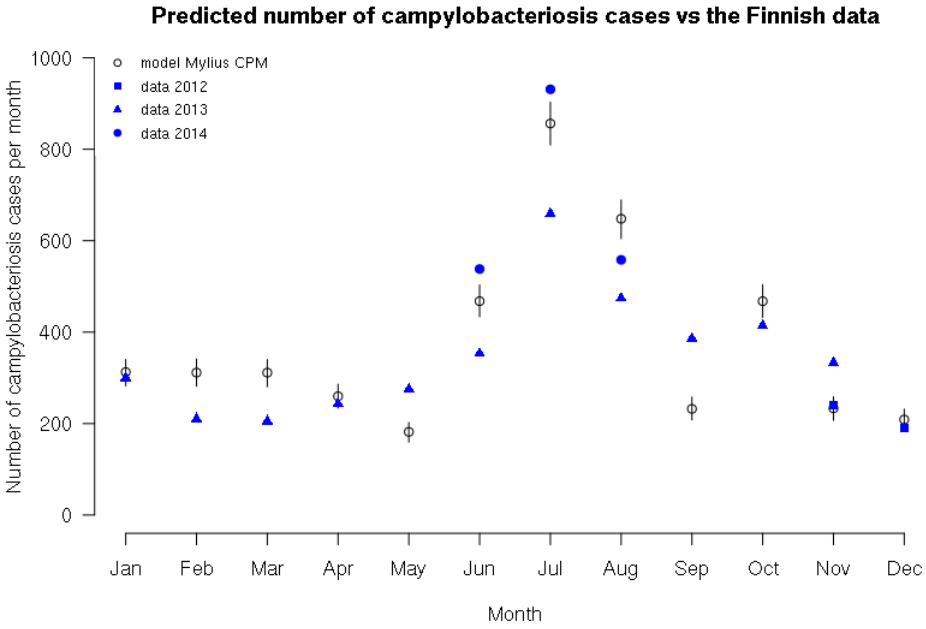
Upon estimating the number of how many times Finnish people eat chicken, the estimated number from the combined model with Christensen respective Mylius CPM was 2 143 859 respective 5 120 741. For example, the combined model with Christensen CPM estimates that there are 2 143 859 times the Finnish people eat chicken regardless of month. With the values from the MCMC sampling of the posterior probability of becoming ill and for the estimation of number of how many Finnish people eat chicken, the predictive posterior for the amount of (reported) campylobacteriosis cases was easily "sampled", i.e. calculated given the sampled values.

Since there are two different CPMs (which results in two different probabilities of becoming ill based on human challenge data), there are two different predictions of amount of (reported) campylobacteriosis cases. Furthermore, since there are uncertainty both in the probability of becoming ill and in the number of how many Finnish people eat chicken, the uncertainty is naturally propagated to the predictions as well. The predictions are to be compared with the Finnish campylobacteriosis data [9].

While the uncertainty intervals of the monthly predicted numbers of (reported) campylobacteriosis cases often fail to cover the Finnish campylobacteriosis data, the predictions clearly follow the same trend as the data with a peak in July. This could be seen in both cases of combined models with Christensen CPM respective Mylius CPM (Figure 10).



(a) Combined model with Christensen.



(b) Combined model with Mylius CPM.

Figure 10: Monthly predictions of number of reported campylobacteriosis cases for the combined model (empty circles). For comparison, the data from the Finnish Institute for Health and Welfare [9] is added to the plot. The data came from the years 2012-2014, corresponding to the data used by Mikkela et al. The blue squares represent the data from the year 2012. The blue triangles represent data from the year 2013. Lastly, the 2014 data are represented by blue circles. 29

4.3.3 Sensitivity analysis

As a part of the uncertainty analysis, a sensitivity analysis is needed in order to investigate and identify the sources that contribute to uncertainty. The aim of sensitivity analysis is to evaluate the effect of model uncertainty on uncertainty in output. This is done by two sensitivity analyses. The first to identify which parameter that has the largest contribution to uncertainty in output. Sensitivity is evaluated on six model outputs for the month of July. July is chosen since this is the month with most cases of infection with Campylobacteriosis.

The second sensitivity analysis is done to see how model output changed depending on the choice of consumer phase model: the Christensen CPM and the Mylius CPM. The approach for sensitivity analysis for a given CPM is as follows:

- Six model outputs are chosen as representative of different stages of the infection process: the seasonal prevalence (pf), the average dose (dose_pred_mean), the mean predicted probability of becoming infected under human challenge respective outbreak, and the mean predicted probability of becoming ill under human challenge respective outbreak.
- A suitable group of parameters is chosen and will be used as the predictors.
- In order to perform a sensitivity analysis, we create adaptive spline surface model (R-package `BASS`) using the chosen parameters and one of the six chosen outputs. This is repeated six times for each of the six outputs.
- A sensitivity analysis is then performed on each of the six adaptive spline surface models.

The R-package `BASS` is used for the sensitivity analysis. In total, the sensitivity analysis was carried out twelve times (six times for each of the two combined models) and ten parameters or variables with the highest first order indices respective total indices are included in the results. This produced in total 24 plots illustrating the sensitivity analyses (Figures 11, 12, 13 and 14).

Overall, there is no prominent parameter that turns up in the analyses in terms of first order indices, i.e. proportion variance, with most of the indices fall below 0.2 in the cases of combined Christensen model (Figure 11) and below 0.1 in the ones with combined Mylius model (Figure 13). With the output being prevalance (pf) the variable prevalence within food batches (pw) has a first order index higher than 60 % respective 30 % in the combined Christensen model respective combined Mylius model. This is no surprise since the prevalence is the product of the within-batch prevalence and between-batch prevalence. Similar result regarding the output being prevalence could also be seen in the case of total indices.

As for total indices, no clear overall pattern could be observed though there are some parameters with a higher uncertainty impact on the outputs. One example is that in the case of output of predicted mean dose the hyperparameter for the predicted concentration (sbd) was shown to have a higher impact on the output in both cases with Christensen respective Mylius (Figures 12 and 14).

Regarding predictions of infection and illness using the combined Mylius model as the output the following parameters could be shown to have higher impact: within-batch prevalence (pw), the hyperparameter for the predicted concentration (τ_w), hyperparameters for the transfer rate of chicken to hand respective to board ($s.t_{CH}$ respective $t.t_{CB}$), the strain mean respective host mean of measure of infectivity respective pathogenicity as well as the variation of infectivity

respective pathogenicity (*mu.w*, *z1* and *z2*. See Teunis et al. [31] for more details) (Figures 12 and 14).

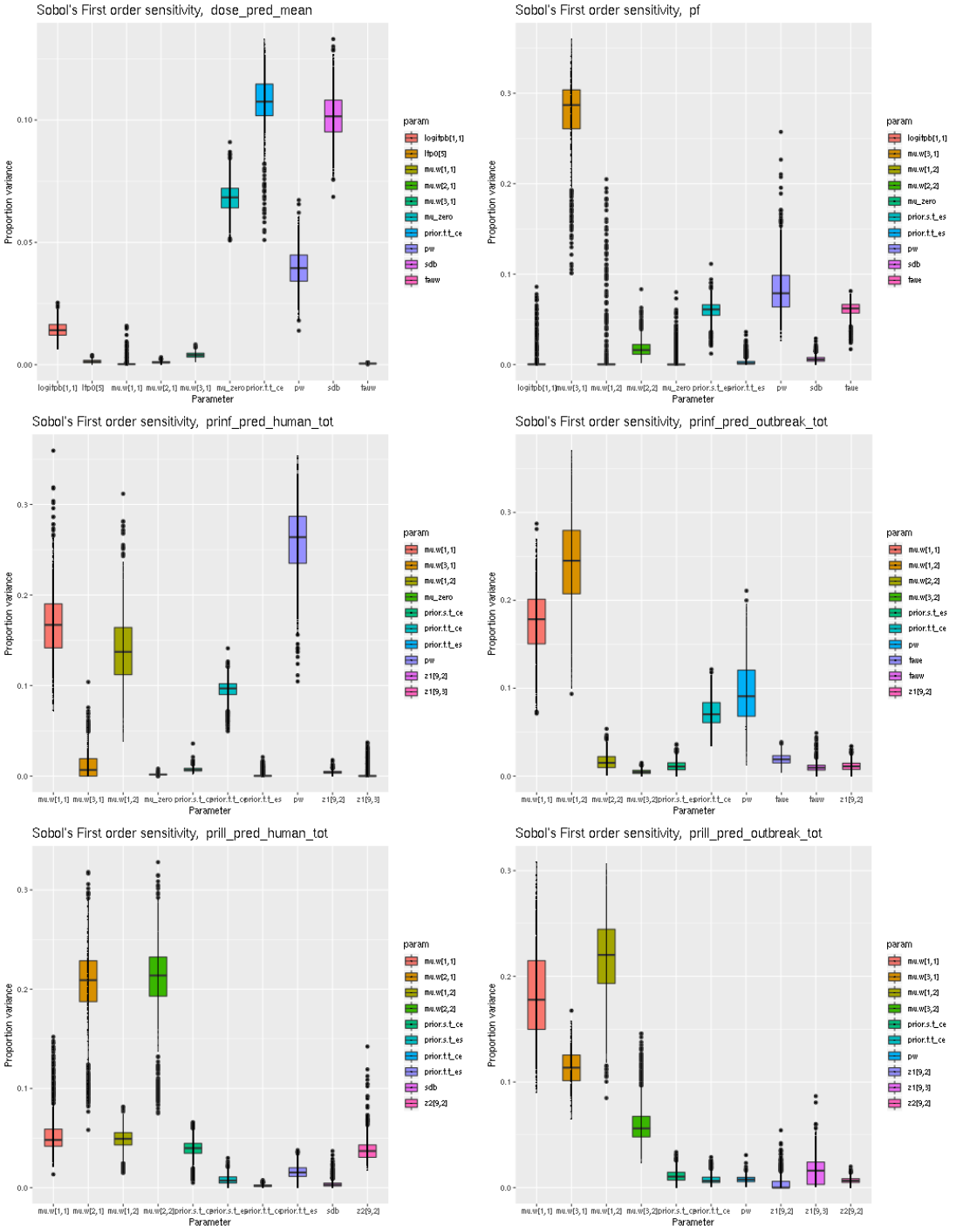


Figure 11: Sensitivity analysis on the combined Christensen model. The ten predictors with the highest first order indices (proportion variance) are shown for each of the six different responses. This was carried out with R-package `BASS`.

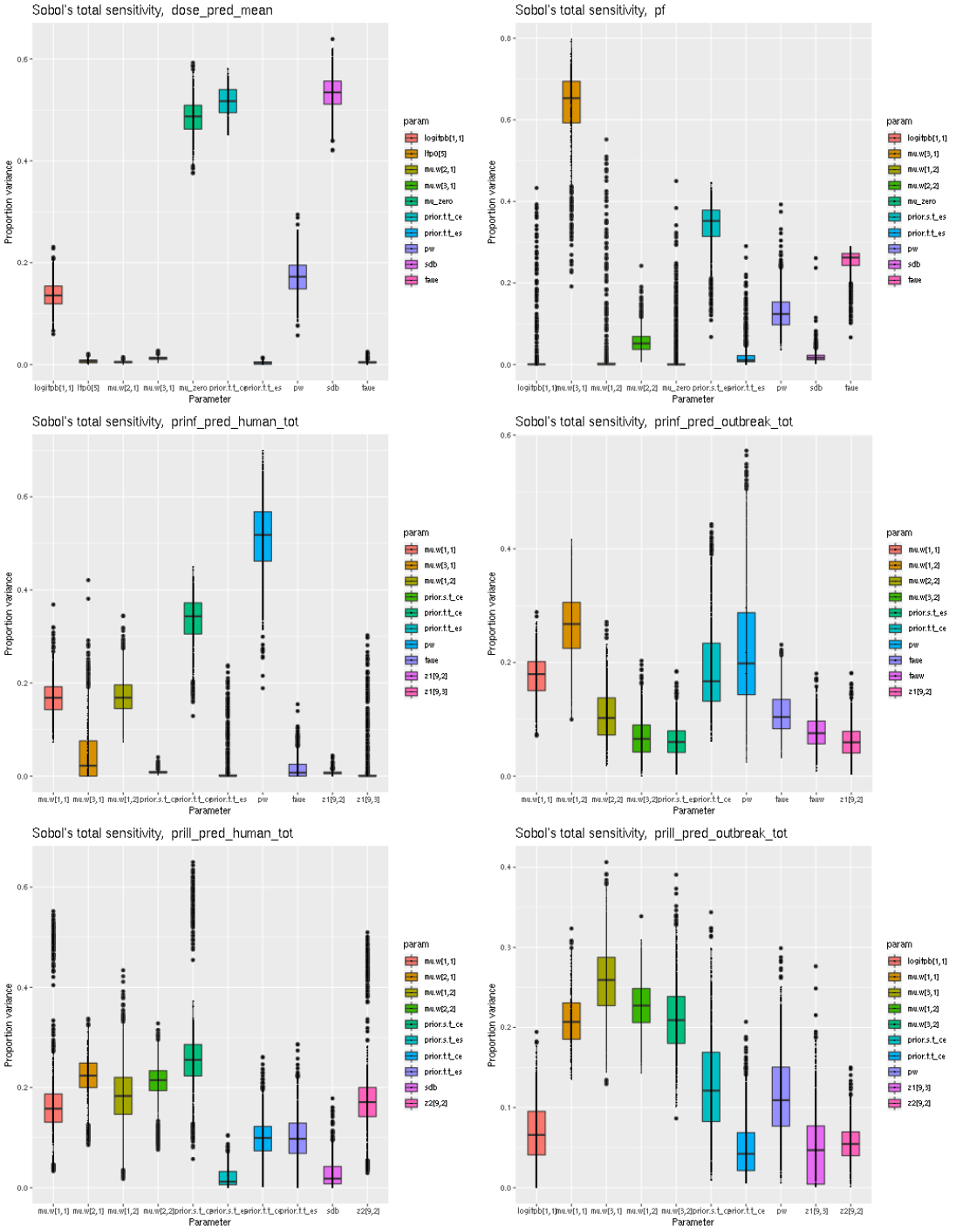


Figure 12: Sensitivity analysis on the combined Christensen model. The ten predictors with the highest total indices (proportion variance) are shown for each of the six different responses. This was carried out with R-package `BASS`.

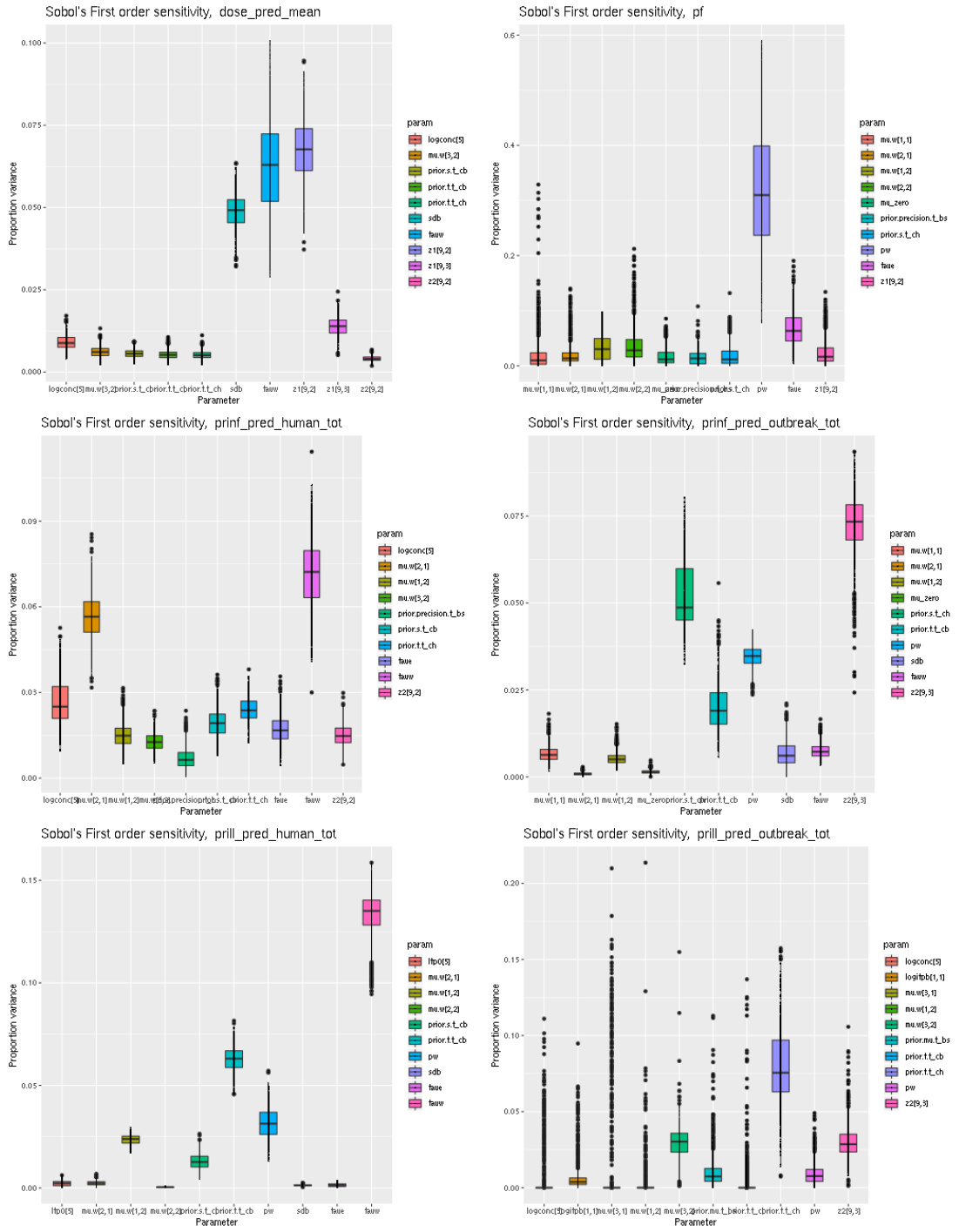


Figure 13: Sensitivity analysis on the combined Mylius model. The ten predictors with the first order indices (proportion variance) are shown for each of the six different responses. This was carried out with R-package `BASS`.

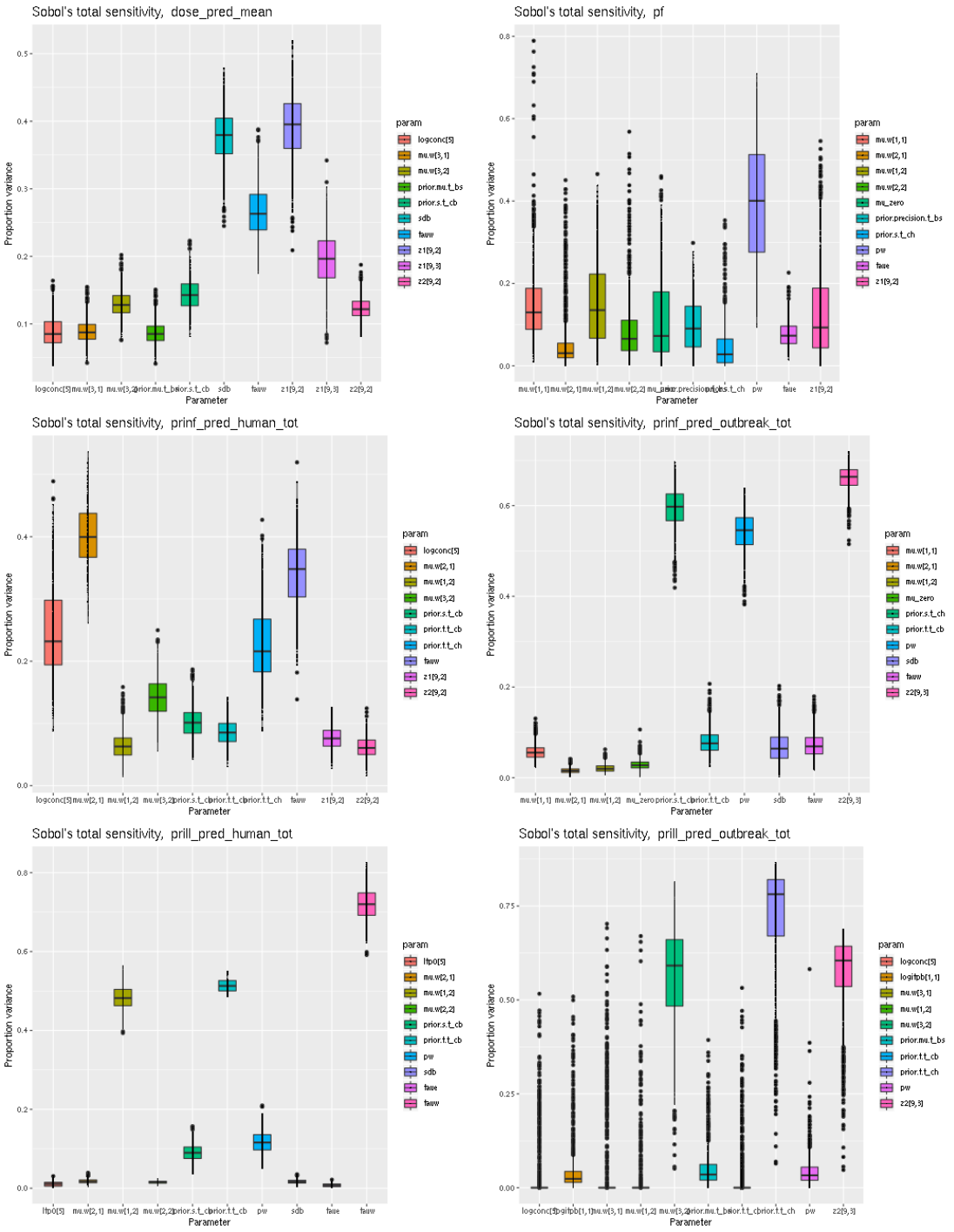


Figure 14: Sensitivity analysis on the combined Mylius model. The ten predictors with the highest total indices (proportion variance) are shown for each of the six different responses. This was carried out with R-package `BASS`.

5 Discussion

5.1 Bayesian model calibration of multiple linked models

This thesis performs an uncertainty analysis on a QMRA. The QMRA assessment model was created by combining a chicken meat contamination model in the primary production (prevalence model), a CPM model and a dose-response model. Those models were identified and implemented in a Bayesian framework to make it possible to quantify epistemic uncertainty by Bayesian model calibration, which allows for uncertainty to be quantified using subjective probability. To avoid slow convergence of MCMC chains, Bayesian model calibration was first done in each of the models with associated data sets, and then by integrating the models into one combined model, but using the posterior from the individual calibrations as priors. This was for the purpose of preserving the characterisation of the already well-adjusted prevalence model and the dose-response model. This approach allowed for estimation of parameters in the third model for which no specific data set were available and it resulted in the assessment model in one probabilistic framework from which it is possible to continue sampling from the posterior. Two different CPMs were considered and therefore the work has resulted in two different combined models which represents QMRA for Campylobacter in a probabilistic uncertainty analysis.

The step-wise approach taken for calibration resulted in a successful preservation of the parameter distributions for the parameters of the individual calibrated models, i.e. the parameters follow the same distribution as before in the individual stage models after combining the models (Figures 20 and 22). The preservation was kept for both CPMs (with Christensen CPM respective Mylius CPM).

One could discuss whether it is good to use informed priors in the combined models and whether it "locks down" the models too much. I used the informed priors because the prevalence and dose-response models were considered as already calibrated by their respective data, and I am not interested to let the uncertainty (both aleatory and epistemic) in the CPMs to be propagated into those models. But had the models not been well-adjusted and there were lot of data available for the CPMs, one might choose another approach, such as using flattened posteriors as priors. The problem is then how and by how much to flatten the posterior. Without using the informed priors while combining the stage models, there is a possibility that the uncertainty from the CPM would flow into the prevalence and dose-response models but this has not been studied.

5.2 Comparing CPMs based on Finnish cases data

During the comparison of the predicted number of campylobacteriosis cases of both models to the corresponding data provided by the Finnish National Institute for Health and Welfare, it is observed that the predictions in the combined Christensen model respective Mylius model follow the same trend as the Finnish data. The trend in the number of cases is highly correlated with the trend in observed prevalences as slaughter houses, but still the change in predictions of the number of cases is not always in the same direction. Thus, the different CPMs models adjusts the probability of becoming infected upwards and downwards everything else equal. A reason could be that they react differently to the observed concentration in chicken.

Although, in terms of accuracy, neither combined model produced satisfactory predictions with uncertainty intervals that cover the reported cases of campylobacteriosis. The predictions are made assuming that the number of people eating chicken every month is treated as fixed, where

values were chosen to improve the fit between model predictions and data. Consequently the two CPMs resulted in different estimates of the number of chicken eaters. Considering variability and uncertainty about the number of consumers, uncertainty in predictions is expected to be larger. The results just mentioned also might be a possible consequence of using both bottom up and top down data where the top down (i.e. cases to exposure of Campylobacter) is very much dependent of reporting system and multiple sources of infection which were not covered in this thesis.

A limitation of this approach is also that the campylobacteriosis data includes all cases with various sources of infection and different ways of contamination, i.e. not only cases associated to raw chicken meat and the ways the meat being prepared in kitchen according to two CPM models used in this thesis. Furthermore, underreporting, which is extensive in Sweden [30], was not considered in this thesis. A way to improve the estimation of the consumption frequency could be to use production data in combination with dietary surveys.

To limit the work in this thesis, two CPMs out the eight CPMs in the article by Nauta et al. [22] were included. It would be interesting to include other CPMs in this analysis, especially if there are CPMs with a lot of data for the transfer rates. The resulting posterior distributions for the parameters of these two models (Tables 10 and 11 in Appendix B) can be used in future QMRA.

5.3 Reproducing models

The prevalence and dose-response model were reproduced from code in the respective publication. One model were transferred from bugs to JAGs, a process resulting in some modifications of the code. In some cases, data generated errors. In other cases, there were errors in the published material, which could be fixed. The turkey part of the prevalence model was omitted due to a computational issue, which could not be solved within the limit of this thesis. The chicken part and turkey part of the prevalence model is separated, it the turkey part is therefore not expected to have any major impact on the results obtained in this thesis.

5.4 Challenges with sensitivity analysis

No conclusion could be drawn from the sensitivity analysis, since it is not clear whether there are parameters with big impact on uncertainty in the outputs of the combined models. It is difficult to make clear conclusions from the sensitivity analysis, and weather this was a result from the chosen method (meta-model with Sobol indices) or because there were no most highly influential parameters. More refined approaches are needed for sensitivity analysis to evaluate influence of uncertainty, including ways to deal with aleatory uncertainty. The group of chosen parameters could also be altered to include variables, for example, dose and prevalence which I instead used as outputs in my analysis. Serving size and concentration might also be of interest to be included in the analysis.

6 Conclusion

In this thesis I demonstrate a way to combine models for risk assessment in a way that allows for quantification of epistemic uncertainty and continuous learning from new data. A challenge has been to combine the models, and I show that combining the different individual stage models, using informed priors, was successful in the sense that parameters were not altered after linking the individual stage models and the calibration of additional parameters were made possible. The approach suggested here is based on principles of Bayesian model calibration and can contribute to probabilistic uncertainty analysis in scientific assessments, where statistical models are used to inform quantitative and realistic models of the system being studied. Finally, while sensitivity analysis is important, it was also found that it is a difficult area in need of development.

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Appendix A

Strain	Host	α			β		
		50%	2.5%	97.5%	50%	2.5%	97.5%
81-176	Primate	0.57	0.17	4.00	0.69	0.061	5.20
78-37	Primate	0.40	0.043	3.64	0.54	0.049	4.56
v212x	Primate	0.47	0.093	3.80	0.60	0.053	4.87
81-176	Human	0.65	0.21	4.17	0.72	0.065	5.54
A3249	Human	0.098	0.052	0.15	0.38	0.055	1.95
CG8421	Human	0.78	0.27	4.50	0.80	0.067	6.12
-	Outbreak	0.53	0.11	3.43	0.94	0.075	6.92
-	Outbreak	0.27	0.058	2.63	0.49	0.049	3.87
81-176	Outbreak	0.22	0.044	2.51	0.50	0.052	3.84
-	Outbreak	0.80	0.17	4.87	0.89	0.082	6.66
pred	Challenge	0.37	0.029	3.44	0.51	0.047	4.29
pred	Outbreak	0.37	0.029	3.55	0.51	0.046	4.28

		r			η		
		50%	2.5%	97.5%	50%	2.5%	97.5%
81-176	Primate	0.042	0.028	0.06	0.81	0.16	3.71
78-37	Primate	0.1	0.01	1.09	1.2	0.18	7.43
v212x	Primate	0.062	0.024	0.14	0.92	0.17	4.67
81-176	Human	0.056	0.041	0.07	0.88	0.16	4.08
A3249	Human	0.019	0.0099	0.03	0.5	0.099	2.58
CG8421	Human	0.15	0.11	0.22	1.5	0.27	7.75
-	Outbreak	0.73	0.14	5.48	0.11	1.2e-09	4.54
-	Outbrea	0.59	0.097	5.35	0.079	1.4e-09	2.74
81-176	Outbreak	0.57	0.077	5.37	0.079	1.3e-09	2.72
-	Outbreak	0.8	0.17	5.57	0.097	1.4e-09	3.81
pred	Challenge	0.061	0.0032	0.98	0.89	0.12	6.49
pred	Outbreak	0.68	0.048	5.66	0.083	1.2e-09	2.84

Table 8: Reproduced result for the dose-response model by Teunis et al. ([31]). Statistics of the parameters for infection (α, β) and illness (r, η), by C. jejuni strain and hist, distinguishing human challenge studies from outbreaks. The bottom rows show predictions based on challenge respective outbreaks.

Appendix B

Parameter	Distribution	1 st parameter of the distri.	2nd parameter of the distr.
logit(pb_1)	Normal	mean = -2.914	sd = 1.775
τ_e	LogNormal	meanlog = -2.196	sdlog = 2.338
e_1	Normal	mean = -0.027	sd = 31.651
p_w	Beta	shape1 = 59.765	shape2 = 40.599
τ_w	Gamma	shape = 17.311	scale = 0.32
μ_0	Normal	mean = -0.348	sd = 0.122
σ_b	Gamma	shape = 25.007	rate = 45.258

Table 9: Informed priors for parameters from the prevalence model [21]. The choice of informed priors are based on posterior from the model with original prior alongside with data

Parameter	Distribution	1 st parameter of the distri.	2nd parameter of the distr.
$t.t_{ce}$	Beta	shape1 = 4.344	shape2 = 40.468
$s.t_{ce}$	Gamma	shape = 3.871	rate = 1.042
$t.t_{es}$	Beta	shape1 = 5.37	shape2 = 29.326
$s.t_{es}$	Gamma	shape = 4.924	rate = 2.413

Table 10: Informed priors for parameters from the Christensen CPM model [22]. The choice of informed priors are based on posterior from the model with original prior alongside with data.

Parameter	Distribution	1 st parameter of the distri.	2nd parameter of the distr.
$t.t_{ch}$	Beta	shape1 = 12.253	shape2 = 164.371
$s.t_{ch}$	Gamma	shape = 8.989	rate = 1.39
$t.t_{cb}$	Beta	shape1 = 4.598	shape2 = 42.579
$s.t_{cb}$	Gamma	shape = 3.996	rate = 1.092
$mu.t_{bs}$	Norm	mean = -0.205	sd = 0.886
$precision.t_{bs}$	Gamma	shape = 5.25	rate = 34.358

Table 11: Informed priors for parameters from the Mylius CPM model [22]. The choice of informed priors are based on posterior from the model with original prior alongside with data.

Parameter	Distribution	Mean	sd
$\mu_{1,strain}$	Normal	-1.606	3.225
$\mu_{1,host}$	Normal	-0.056	3.058
$\mu_{2,strain}$	Normal	2.996	3.531
$\mu_{2,host}$	Normal	0.726	3.201
$\mu_{3,strain}$	Normal	-3.573	6.144
$\mu_{3,host}$	Normal	-0.411	2.998
z_1	Normal	1.739	2.339
z_2	Normal	1.034	2.678
z_2, outbreak only	Normal	1.213	2.449
$logconc$	Normal	4.512	2.576
$logitp_0$	Normal	-2.914	2.011

Table 12: Informed priors for parameters from the dose-response model [31]. The choice of informed priors are based on posterior from the model with original prior alongside with data.

Appendix C

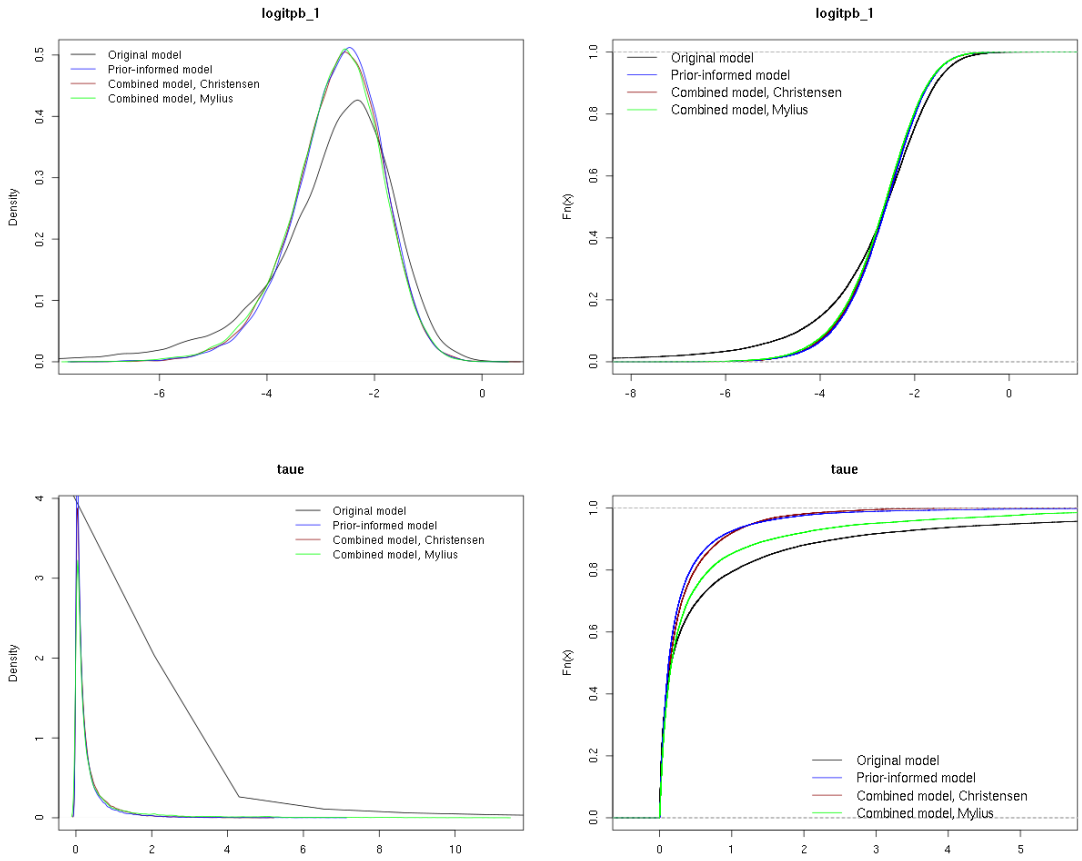

Figure 15: The posterior for the parameters in the prevalence model [21]. Black lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM and green lines for posterior from combined model with informed prior and Mylius CPM.

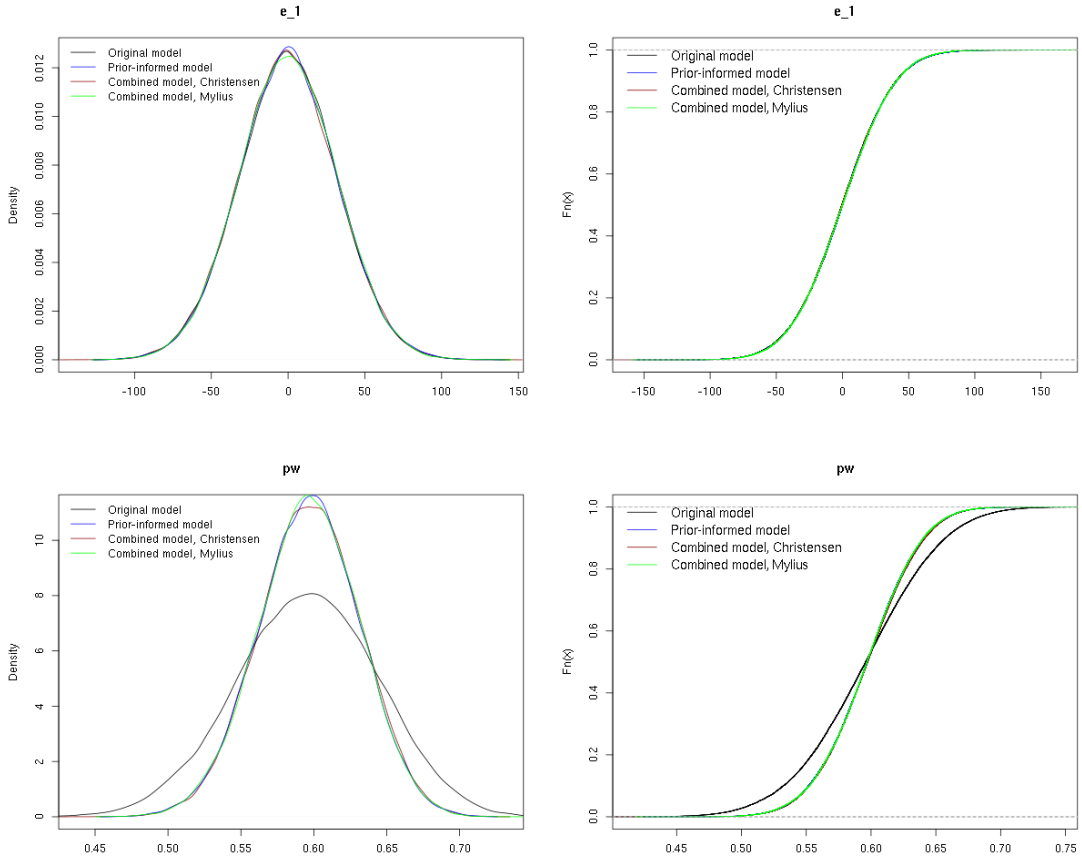

Figure 17: The posterior for the parameters in the prevalence model [21]. Black lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM and green lines for posterior from combined model with informed prior and Mylius CPM.

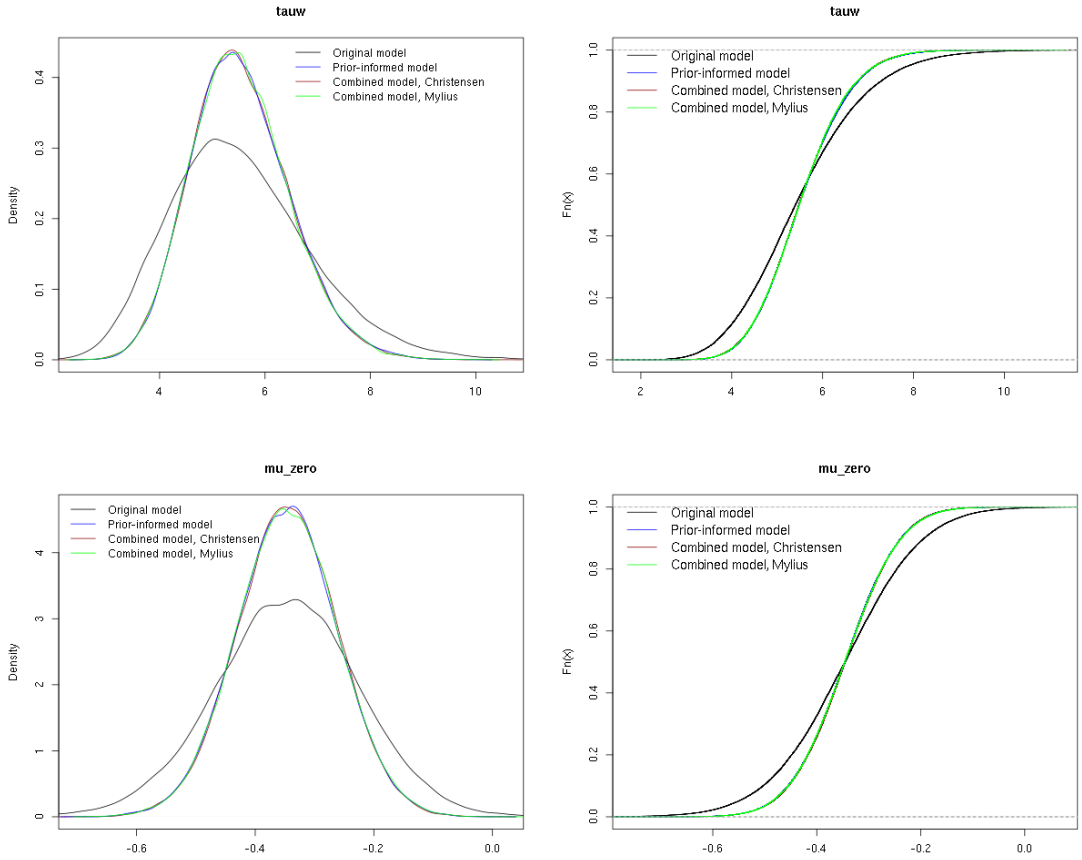

Figure 18: The posterior for the parameters in the prevalence model [21]. Black lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM and green lines for posterior from combined model with informed prior and Mylius CPM.

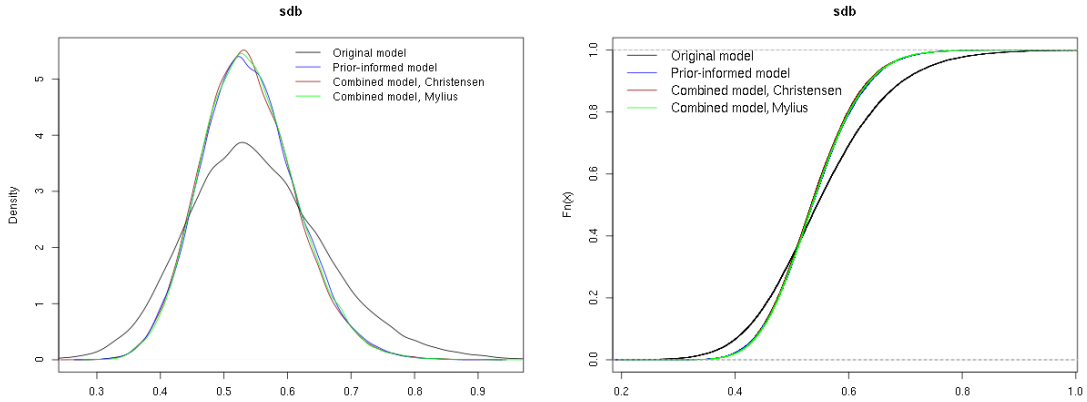

Figure 19: The posterior for the parameters in the prevalence model [21]. Black lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM, and green lines for posterior from combined model with informed prior and Mylius CPM.

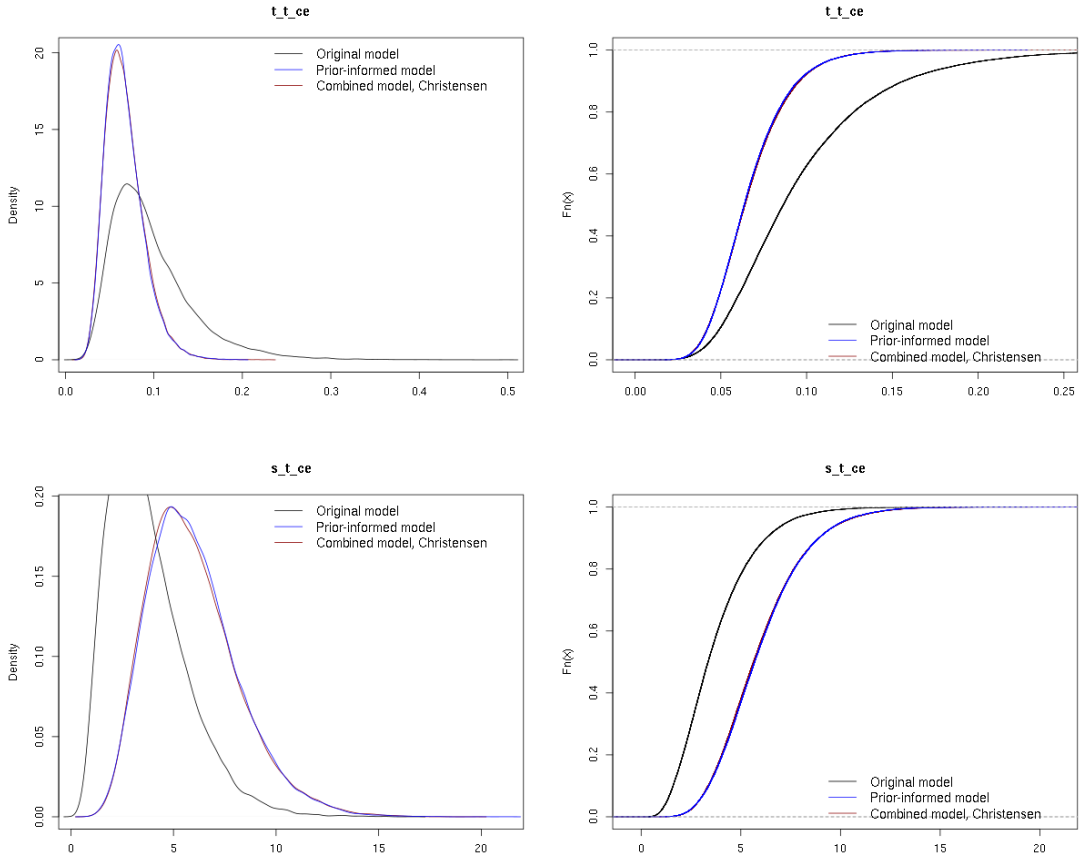

Figure 20: The posterior for the parameters in the Christensen CPM model [22]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior and red lines for posterior from combined model with informed prior and with Christensen CPM.

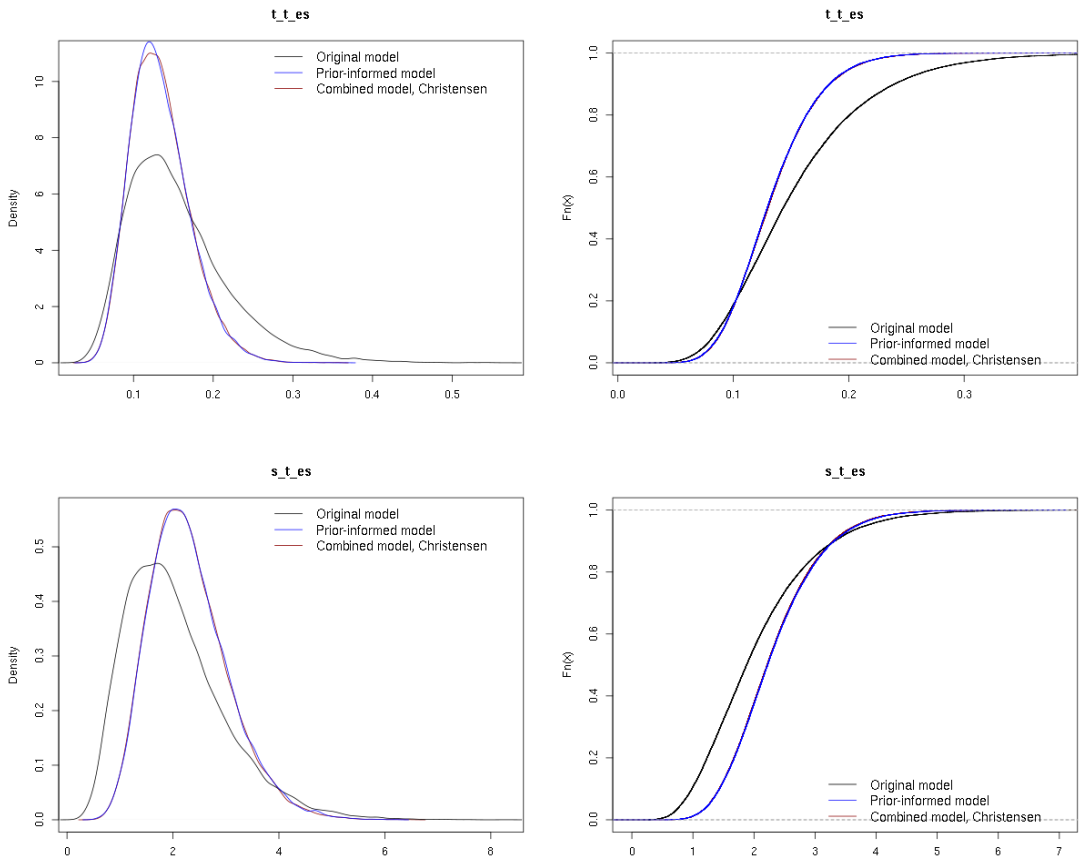

Figure 21: The posterior for the parameters in the Christensen CPM model [22]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior and red lines for posterior from combined model with informed prior and with Christensen CPM.

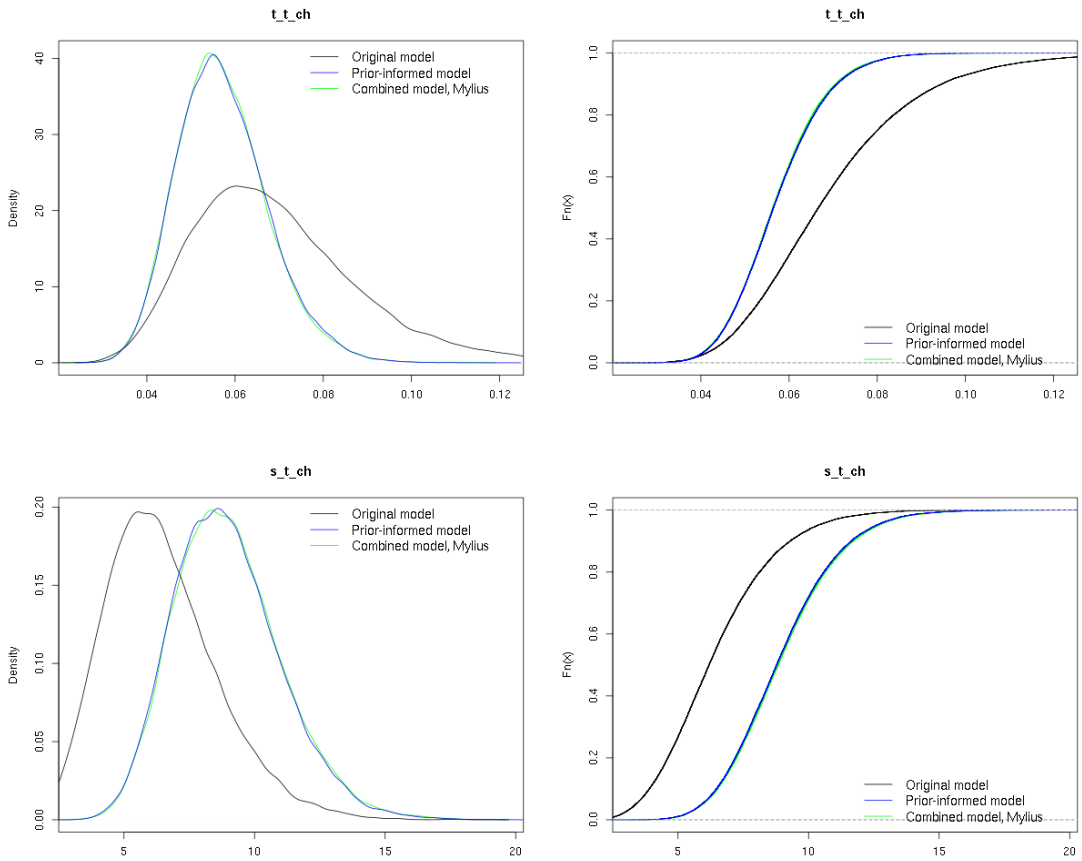

Figure 22: The posterior for the parameters in the Mylius CPM model [22]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior and green lines for posterior from combined model with informed prior and Mylius CPM.

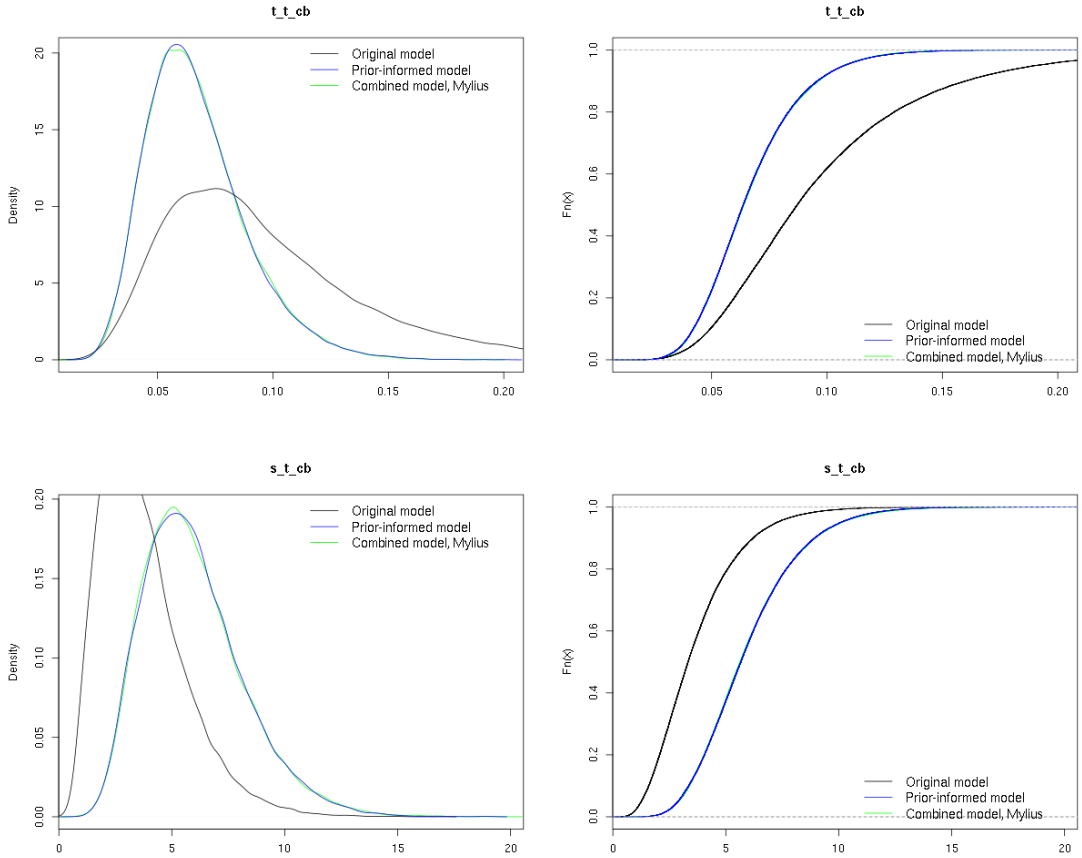

Figure 23: The posterior for the parameters in the Mylius CPM model [22]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior and green lines for posterior from combined model with informed prior and Mylius CPM.

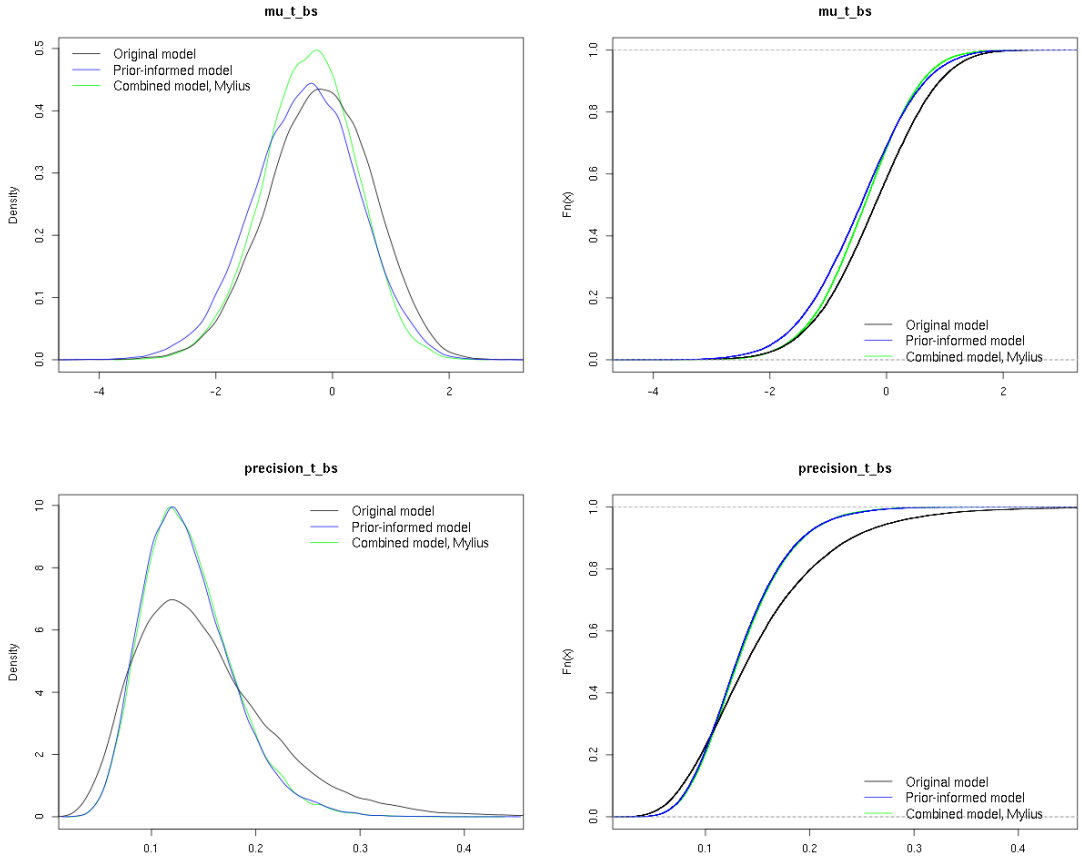

Figure 24: The posterior for the parameters in the Mylius CPM model [22]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior and green lines for posterior from combined model with informed prior and Mylius CPM.

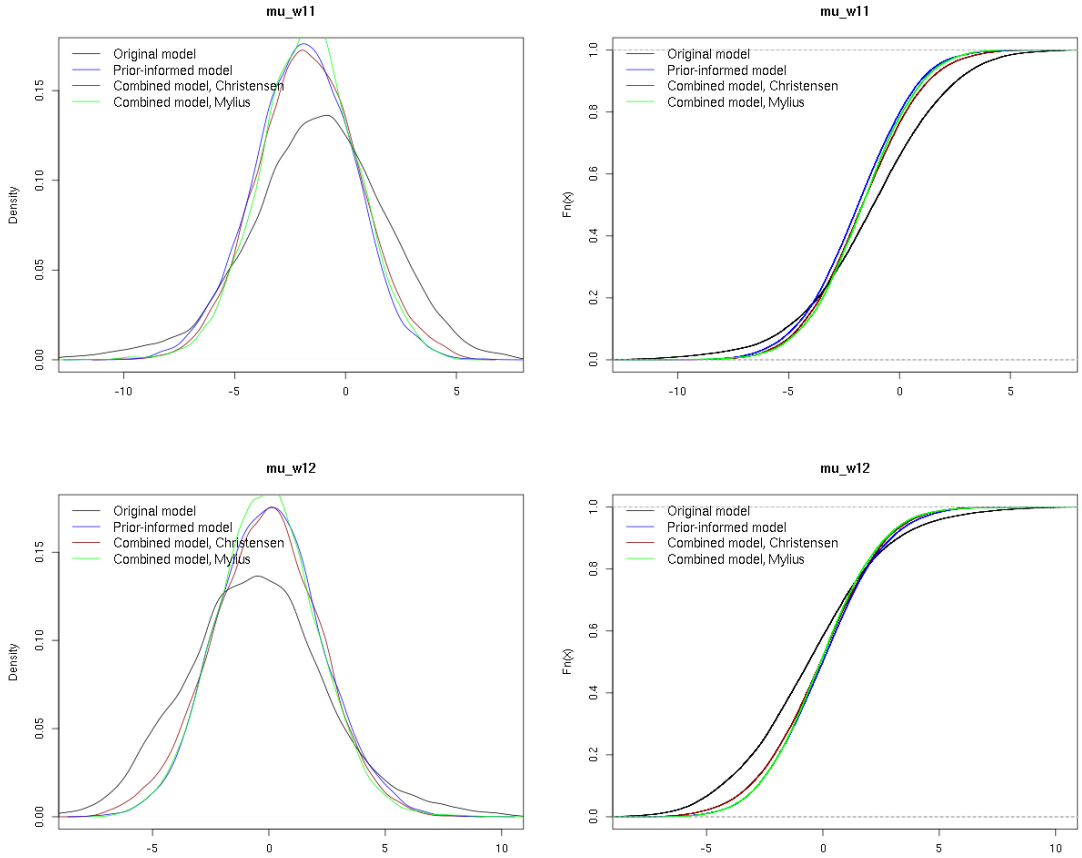

Figure 25: The posterior for the first half set of chosen parameters in the dose-response model [31]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM and green lines for posterior from combined model with informed prior and Mylius CPM.

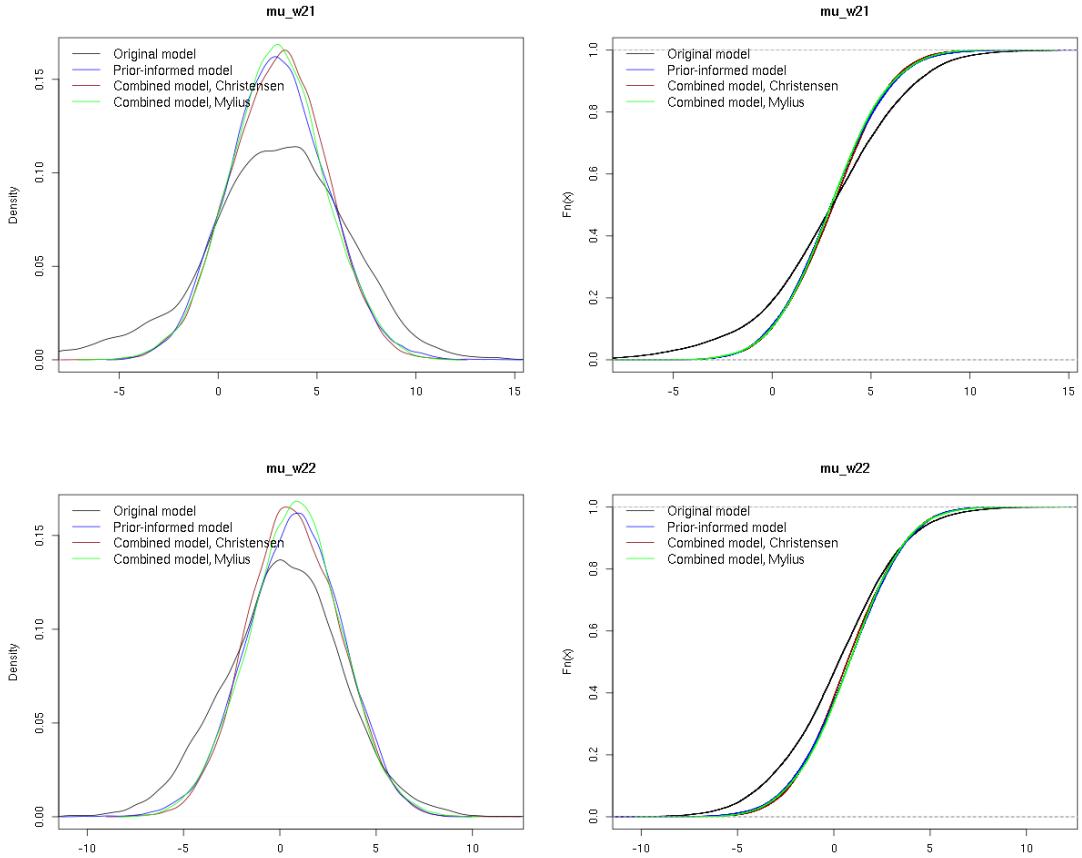

Figure 26: The posterior for the first half set of chosen parameters in the dose-response model [31]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM and green lines for posterior from combined model with informed prior and Mylius CPM.

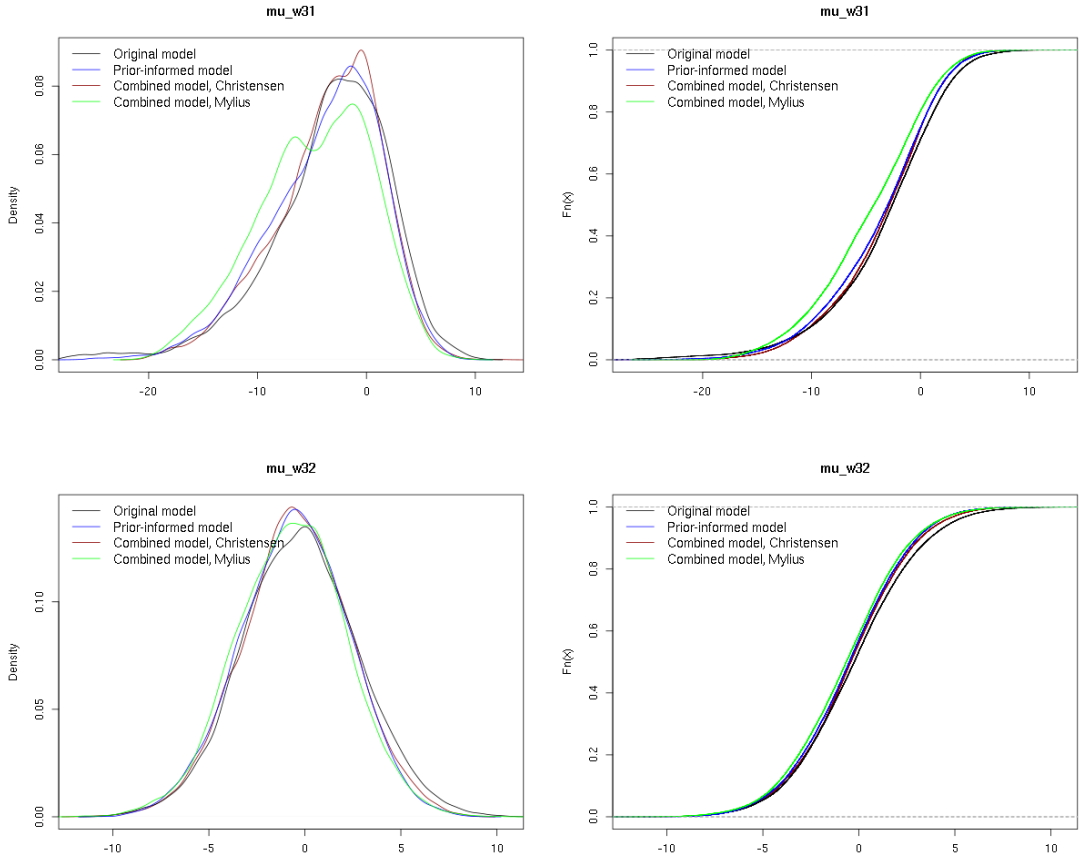

Figure 27: The posterior for the first half set of chosen parameters in the dose-response model [31]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM and green lines for posterior from combined model with informed prior and Mylius CPM.

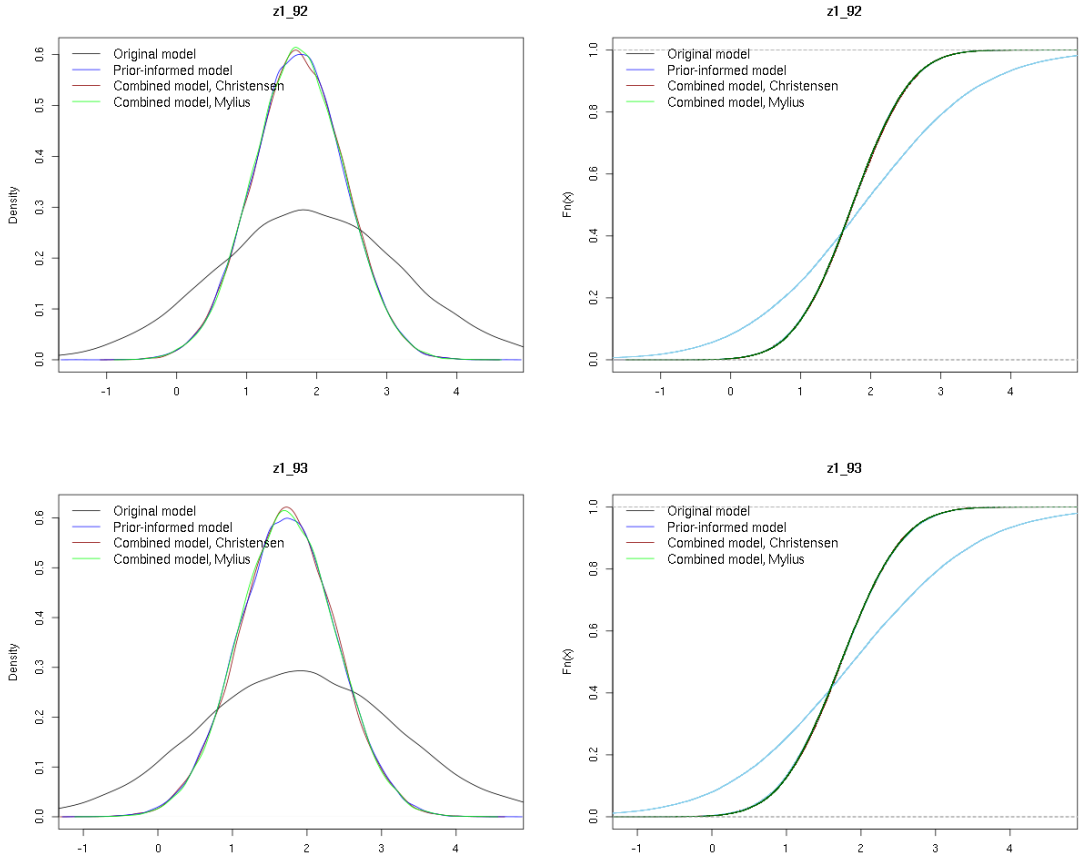

Figure 28: The posterior for the second half set of chosen parameters in the dose-response model/submodel [31]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM and green lines for posterior from combined model with informed prior and Mylius CPM.

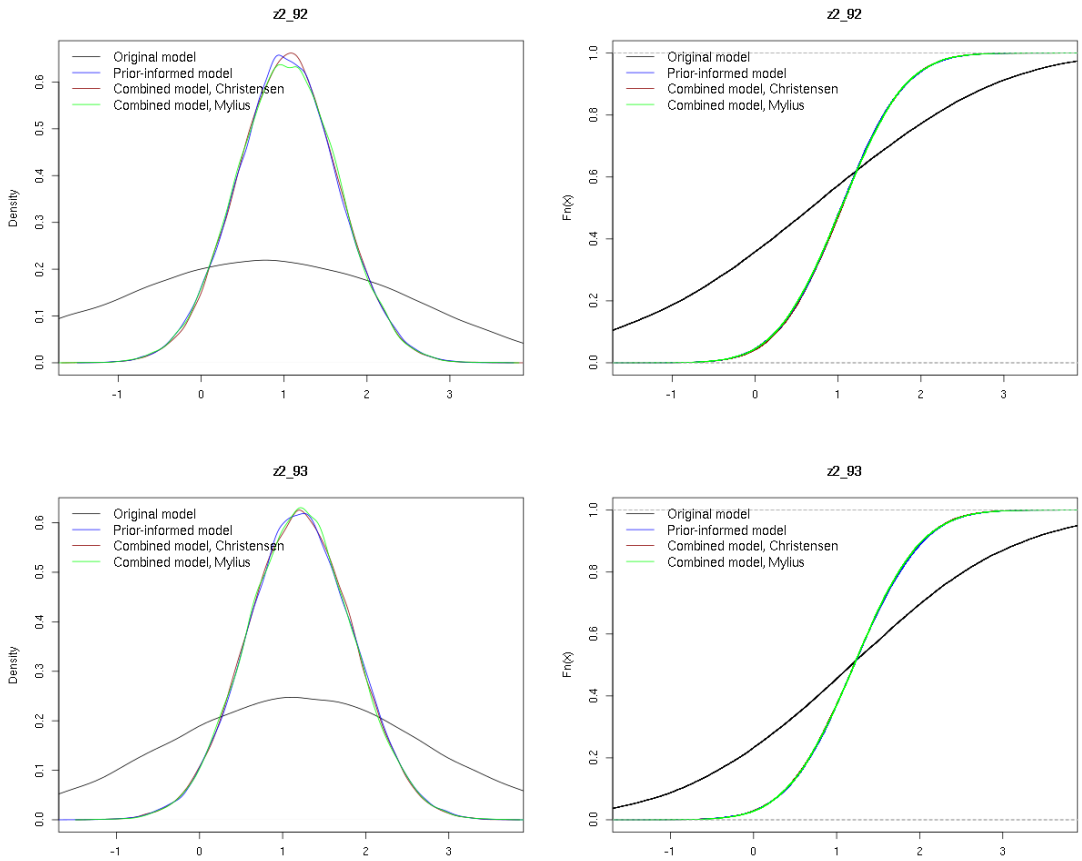

Figure 29: The posterior for the second half set of chosen parameters in the dose-response model/submodel [31]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM and green lines for posterior from combined model with informed prior and Mylius CPM.

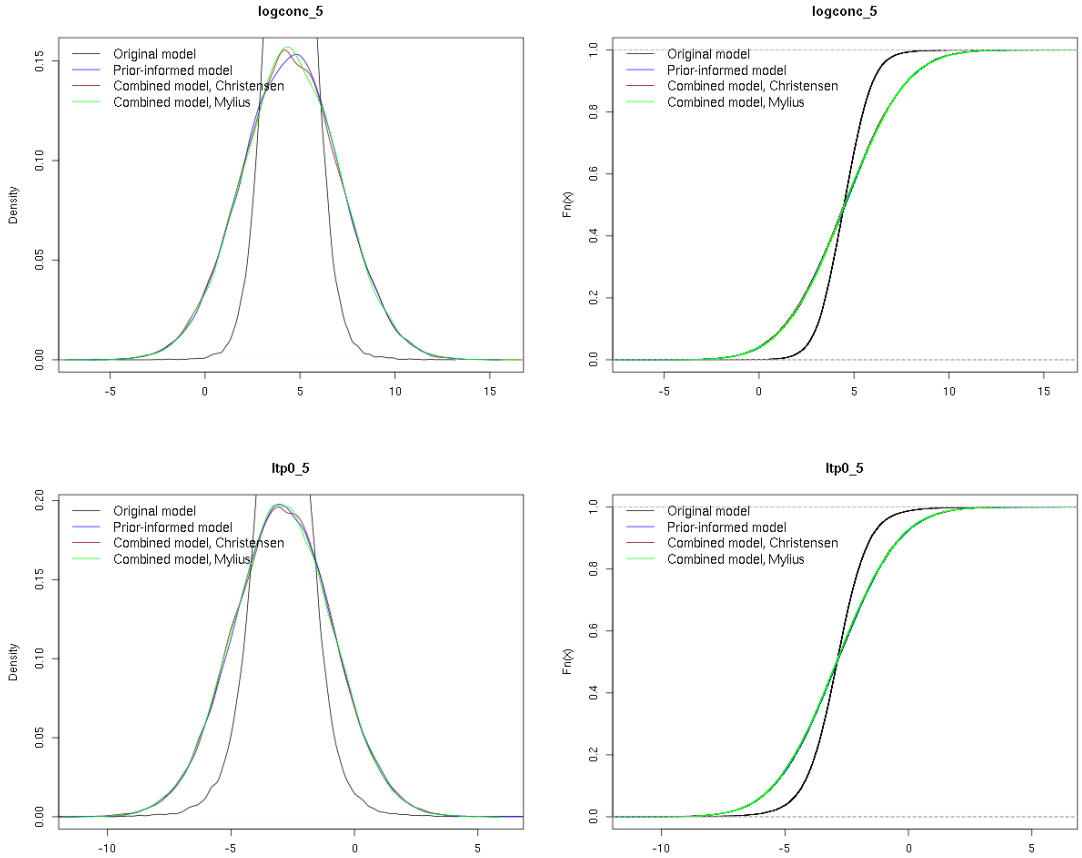

Figure 30: The posterior for the second half set of chosen parameters in the dose-response model/submodel [31]. Dashed blue lines displays posterior from individual models with original prior, blue lines for posterior from individual models with informed prior, red lines for posterior from combined model with informed prior and with Christensen CPM and green lines for posterior from combined model with informed prior and Mylius CPM.