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Disease burden in the Netherlands due to infections with Shiga-toxin producing *Escherichia coli* O157

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Abstract

Infection with Shiga-toxin producing *Escherichia coli* serotype O157 (STEC O157) may lead to a gastro-enteritis (GE) episode. Symptoms can vary from relatively mild watery diarrhoea to a severe form of bloody diarrhoea known as haemorrhagic colitis. In children, and sporadically in adults, the Shiga-toxin may cause the Haemolytic Uraemic syndrome (HUS). Some HUS patients may develop End Stage Renal Disease (ESRD), either directly after the HUS episode or as many as 20 years later. ESRD patients are dependent on renal replacement therapy (dialysis, kidney transplantation) while GE, HUS and ESRD can all lead to premature mortality. Here, the epidemiology of illness associated with STEC O157 in the Netherlands is described on the basis of surveys carried out between 1990 and 2000. All available information is integrated in one public health measure, the Disability Adjusted Life Year (DALY). The mean disease burden associated with STEC O157 in the Dutch population has been estimated through simulation at 116 DALY per year (85 - 160 DALY per year using a 90% confidence interval). The disease burden is also highly variable. Mortality due to HUS (58 DALY), mortality due to ESRD (21 DALY) and dialysis due to ESRD (21 DALY) constitute the main determinants of disease burden. Scenario analysis was used to evaluate the influence of uncertain assumptions in the above calculations. In all scenarios, the estimated disease burden was within the above-mentioned confidence interval.

Preface

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Symbol list

Parameters:

e	Individual life span	year
a	Age	year
ν	Morbidity rate	per year
N	Incidence	per year
t	Observation or person time	year
w	Severity weight	
π	Binomial probability	
ψ	Attributable proportion	

Level of observation:

No subscript: population; subscript GP: general practitioner, subscript LS: laboratory surveillance;

Other subscripts:

i	Index for age class
j	Index for type of illness: no index: total Dutch population 1999 (CBS), G = gastro-enteritis, S = STEC O157 associated illness, B = bloody diarrhoea, W = non-bloody diarrhoea, A = asymptomatic infection, H = haemolytic uraemic syndrome, E = end-stage renal disease, M = mortality, TX = kidney transplantation, FG = functioning graft, D = dialysis; R = recovered renal function, * = participants in case-control study
u	index for iteration number
s	index for simulation number
z	dummy variable

Abbreviations

DALY	Disability Adjusted Life Years
ESRD	end stage renal disease
GE	gastroenteritis
(D+) HUS	(diarrhoea-associated) haemolytic uraemic syndrome
NIVEL	Netherlands Institute of Primary Health Care
PYN	pyelonephritis
Renine	Renal Replacement Registry of the Netherlands
SENSOR	population based cohort study on gastroenteritis
ST	Shiga-toxin
STEC O157	Shiga toxin producing *Escherichia coli* serotype O157
TTP	thrombotic thrombocytopenic purpura
TX	renal transplantation
YLD	Years Lived with a Disability
YLL	Years of Life Lost

Probability density functions

Beta (α, β) = $f(x) = \frac{x^{\alpha-1}(1-x)^{\beta}-1}{B(\alpha,\beta)}$ where $B(\alpha,\beta) = \int_0^1 t^{\alpha-1}(1-t)^{\beta-1}\,dt$

Binomial (n, π): $f(x) = \binom{n}{x}\pi^x(1-\pi)^{n-1}$

Gamma (α, β): $f(x) = \frac{\beta^{-\alpha}x^{\alpha-1}\exp\left(-\frac{x}{\beta}\right)}{\Gamma(\alpha)}$ where $\Gamma(\alpha)$ = Euler's Gamma function

NegBin(s,π): $f(x) = \binom{s+x-1}{x}\pi^s(1-\pi)^x$

Poisson (λ): $f(x) = \frac{e^{-\lambda}\lambda^x}{x!}$

Uniform (min,max): $f(x) = \frac{1}{\max-\min}$

Weibull (α, β): $f(x) = \alpha\beta^{-\alpha}x^{\alpha-1}\exp\left(-\left(\frac{x}{\beta}\right)^{\alpha}\right)$

Contents

Samenvatting

Infectie met Shiga-toxine producerende *Escherichia coli* serotype O157 (STEC O157) leidt meestal tot een episode van acute gastro-enteritis (GE). De symptomen variëren van relatief milde, waterige diarree tot een ernstige vorm van bloederige diarree die bekend is als hemorragische colitis. In kinderen, en sporadisch in volwassenen, kan het Shiga-toxine aanleiding geven tot het Hemolytisch Uremisch syndroom (HUS). Sommige HUS patiënten ontwikkelen chronisch nierfalen, leidend tot uiteindelijk terminale nierinsufficiëntie (End Stage Renal Disease - ESRD), hetzij direct ofwel tot 20 jaar of meer na de HUS episode. ESRD patiënten zijn afhankelijk van niervervangende therapie (dialyse of niertransplantatie). Zowel GE, HUS als ESRD kunnen leiden tot voortijdige sterfte. Dit rapport beschrijft de epidemiologie van met STEC O157 geassocieerde ziekte in Nederland, gebaseerd op onderzoek in de periode 1990-2000. De beschikbare informatie wordt geïntegreerd in één volksgezondheidsmaat, de Disability Adjusted Life Year (DALY). DALYs zijn de som van het aantal verloren levensjaren ten gevolge van voortijdige sterfte, en het aantal jaren dat met ziekte wordt doorgebracht, gewogen met een factor tussen 0 en 1 voor de ernst van die ziekte. De incidentie van met STEC O157 geassocieerde GE wordt geschat op 1250 gevallen per jaar (mediaan), waarvan ongeveer 180 patiënten hun huisarts bezoeken. Van 40 patiënten wordt uit een voor laboratoriumonderzoek ingezonden fecesmonster STEC O157 geïsoleerd. Het aantal sterfgevallen is erg onzeker, de meest waarschijnlijke waarde is 2 sterfgevallen per 3 jaar, met name onder ouderen. De incidentie van HUS veroorzaakt door STEC O157 in Nederland is ongeveer 22 gevallen per jaar, waarvan 15 kinderen onder 15 jaar. Daarvan leiden gemiddeld 2,5 gevallen per jaar tot ESRD. Naar schatting overlijden 2 patiënten per jaar ten gevolge van HUS, en 1 patiënt per 2 jaar aan de gevolgen van ESRD.
Weegfactoren voor de ernst van GE, HUS en ESRD werden afgeleid uit eerder gepubliceerde studies. De duur van ziekte en levensverwachting van fatale gevallen werden uit verschillende epidemiologische onderzoekingen afgeleid. Het beloop van patiënten met ESRD werd gebaseerd op de registratie van de Stichting Renine.
Combinatie van bovengenoemde informatie leidt tot een schatting van de ziektelast door STEC O157 in de Nederlandse bevolking. Onzekerheid en variabiliteit in de epidemiologische informatie zijn expliciet bij de analyse betrokken door middel van Monte Carlo simulatie en gevoeligheidsanalyse. De geschatte gemiddelde ziektelast bedraagt ca. 116 (90% betrouwbaarheidsinterval 85-160) DALY per jaar. De belangrijkste bijdragen worden geleverd door sterfte ten gevolge van HUS (58 DALY), sterfte ten gevolge van ESRD (21 DALY), en morbiditeit door dialyse ten gevolge van ESRD (21 DALY). (Bloederige) diarree (7 DALY) levert eveneens bijdragen aan de ziekte last. Vergelijking met de resultaten van een eerder onderzoek geeft aan dat de ziektelast van thermofiele *Campylobacter* spp. in absolute zin groter is dan die van STEC O157 (1400 vs. 116 DALY per jaar) maar per geval van primaire gastroenteritis minder ernstig. De invloed van onzekere aannames in de berekeningen werd geëvalueerd met behulp van scenario analyse. In alle scenario's was de berekende ziektelast binnen het bovengenoemde betrouwbaarheidsinterval.

Summary

Infection with Shiga-toxin producing *Escherichia coli* serotype O157 (STEC O157) may lead to a gastro-enteritis (GE) episode. Symptoms may vary from relatively mild watery diarrhoea to a severe form of bloody diarrhoea known as haemorrhagic colitis. In children, and sporadically in adults, the Shiga-toxin may lead to the Haemolytic Uraemic syndrome (HUS). Some HUS patients may develop chronic renal failure, ultimately leading to terminal renal insufficiency (End Stage Renal Disease - ESRD), either directly after the HUS episode or as many as 20 years later. ESRD patients are dependent on renal replacement therapy (dialysis, kidney transplantation). GE, HUS and ESRD all may lead to premature mortality.
Here, the epidemiology of illness associated with STEC O157 in the Netherlands is described on the basis of surveys carried out between 1990 and 2000.All available information is integrated in one public health measure, the Disability Adjusted Life Year (DALY). DALYs are the sum of Years of Life Lost by premature mortality and Years Lived with Disability, weighed with a factor between 0 and 1 for the severity of the illness.
The incidence of STEC O157 associated GE is estimated at 1250 cases per year (median), of which approximately 180 patients visit their general practitioner. A faecal sample is sent to a laboratory and tested positive for STEC O157 for 40 patients. The number of fatal cases is highly uncertain, with a most likely value of 2 per 3 years, mainly among the elderly. The incidence of STEC O157 associated HUS in the Netherlands is 22 cases per year, of which 15 in children under 15 years. 2.5 HUS patients per year develop ESRD. The number of fatalities associated with HUS is estimated as 2 per year, and 1 patient per 2 years dies as a consequence of ESRD.
Severity weights for GE, HUS and ESRD were derived from published studies. Duration of disease and expected life span of fatal cases were obtained from different epidemiological studies. The clinical course of ESRD patients was based on the Dutch Renal Replacement registry Renine.
Combining this information, the disease burden of illness associated with STEC O157 in the Dutch population can be estimated. Uncertainty and variability in the epidemiological information are explicitly taken into account in the analysis by Monte Carlo simulation, and by sensitivity analysis. The mean disease burden is 116 (90% confidence interval 85-160) DALY per year Mortality due to HUS (58 DALY), mortality due to ESRD (21 DALY) and dialysis due to ESRD (21 DALY) constitute the main determinants of disease burden. (Bloody) diarrhoea (7 DALY) also adds to the disease burden. Comparison with a previous study demonstrates that the disease burden associated with thermophilic *Campylobacter* spp. is higher in an absolute sense (1400 vs. 100 DALY per year) but substantially lower per primary case of gastro-enteritis. Scenario analysis was used to evaluate the influence of uncertain assumptions in the above calculations. In all scenarios, the estimated disease burden was within the above-mentioned confidence interval.

1. Introduction

Recent food safety crises have increased awareness among policy makers and the public of the public health threats of pathogenic microorganisms in the food chain. As a consequence, the organisation of national and international bodies with food safety responsibilities is revised and public health aspects are increasingly important factors in decision-making. The production chain of foods from primary agricultural products to food ready for consumption is increasingly complex and interventions are possible at many different stages of the food pathway. Mathematical risk assessment models are increasingly being used as tools to analyse the effects of possible mitigation strategies, both with respect to their public health impact as well as to their costs. To quantify the public health burden of foodborne illness or the health benefits of a particular intervention measure, it is necessary to account for the wide spectrum of illness that may be associated with foodborne pathogens. Most frequently, the effects are mild and of a self-limiting nature (nausea, vomiting, watery diarrhoea) but more severe manifestations of acute gastrointestinal or systemic disease (bloody diarrhoea, dehydration, sepsis) or complications (Guillain-Barré syndrome, haemolytic uraemic syndrome, reactive arthritis) may occur [47]. Case-fatality ratios of complications may be as high as 10%, but gastroenteritis may also be life threatening, particularly in the elderly [76]. To account for the widely different clinical manifestations of foodborne illness, a uniform health measure is needed. In a previous study [39], the public health indicator “Disability Adjusted Life Years” (DALYs) was used to integrate the health burden of different clinical syndromes associated with thermophilic *Campylobacter* species. DALYs are the sum of life years lost by premature mortality and life years spent in ill health, weighed for the severity of illness. In this study, we present epidemiological data on the incidence of illness associated with Shiga-toxin producing *E. coli* serotype O157 (STEC O157) in the Netherlands, and use the DALY concept to estimate the health burden in the Dutch population.

STEC O157 is the most important serotype in the group of highly pathogenic enterohaemorrhagic *E. coli*. These bacteria are characterised by the ability to produce Shiga-like toxins (ST) after intestinal colonisation. STEC O157 induces a severe form of gastroenteritis, characterised by bloody stools (haemorrhagic colitis) and is also the cause of haemolytic uraemic syndrome (HUS) in young children and sporadically in adults. Cattle are an important reservoir of STEC O157 and beef products as well as raw milk have caused major outbreaks world-wide but the role of other reservoirs such as farm animals is increasingly being recognised. In the Netherlands, only two small outbreaks have been recognised [20,42] and the number of endemic cases is low [86]. However, because the bacteria are present in the food chain, the possibility of outbreaks cannot be ruled out and preventive measures are indicated. For more information, see [17,38,41,49].

The present report is written as an addition to a risk assessment study of STEC O157 in steak tartare [55]. Together, the reports will provide insight in the public health risks of STEC O157 in the food chain in the Netherlands, and will help to decide about risk management options.

2. The disease burden model

2.1 Disability Adjusted Life Years

The different outcomes of infectious disease can be combined in one single measure, the Disability Adjusted Life Year (DALY), following the methodology proposed by Murray and co-workers [53] [54].

$$DALY = YLL + YLD$$

YLL is the number of years of life lost due to mortality and YLD is the number of years lived with a disability, weighted with a factor between 0 and 1 for the severity of the disability. YLL is calculated by accumulation over all fatal cases and all diseases of the expected individual life span (e) at the age of death. Thus:

$$YLL = \Sigma_{\text{all diseases}} \Sigma_{\text{all fatal cases}} (e)$$

We derive the expected life span of fatal cases from the standard life table as reported by Statistics Netherlands, see Appendix 6.

YLD is calculated by accumulation over all cases and all diseases of the product of the duration of the illness (t) and the severity weight (w):

$$YLD = \Sigma_{\text{all diseases}} \Sigma_{\text{all cases}} (t \times w)$$

Information on the incidence of illness and death is typically objective data derived from clinical, epidemiological and surveillance studies, whereas information on severity weights is typically subjective data, derived from elicitation of special panels, of patients suffering from the diseases of concern or from the general population. There is uncertainty and variability in the data used to calculate the disease burden. Here, variability is defined as the inherent randomness of a system under study. Uncertainty is defined as lack of knowledge about the system. Additional data collection can reduce uncertainty but not variability. Both uncertainty and variability can be expressed in a statistical distribution function, but require a different strategy to account for in the analysis. In this study, severity and duration of disease were considered to be variable parameters, whereas all other parameters (related to the incidence of illness and death) were considered to be uncertain. Second order uncertainty (i.e. uncertainty in the parameter estimates of the distribution functions of the variable quantities) was also considered. We use a second order stochastic simulation model to quantify the disease burden of STEC O157 associated illness. The general modelling strategy is illustrated by a simple example in the next paragraph.

2.2 General modelling approach

The model is explained in several steps, starting with the simplest case (no uncertainty, no variability), followed by introduction of variability and then uncertainty. The examples are based on data for bloody diarrhoea and for mortality from gastroenteritis.
The formulas for disease burden are applied in basic notation:

Disability burden YLD = N x t x w /365 (healthy life years per year),
where Incidence of illness N (cases per year)
Duration t (days)
Severity weight w

Mortality burden YLL = d x e (life years per year)
where Incidence of death d (cases per year),
Expected life span e (years)

A. No uncertainty or variability: incidence known, severity and duration constant
First, consider the case that the (observed) incidence of illness is constant, and that all cases in the population can be observed. If a population with these characteristics is followed for many years, the observed number of cases in the population will be constant. The annual disease burden is obtained by calculating the disease burden for each individual patient (i.e. the product of severity and duration) and by summation of these products for all patients. If severity and duration are constant for each patient, the annual disease burden will also be constant and can be represented by a single value.

For example:
N = 1000 cases per year
t = 5.6 days
w = 0.393

YLD = N x t x w = 1000 x 5.6 x 0.393 / 365 = 6.03 per year

If this population would be studied for a long time, the same result would be found each year.

B. Only variability: incidence known, severity and duration variable
Now consider the more realistic case that the incidence **rate** (the average number of cases per year) is constant and the observed incidence follows a random (Poisson) distribution with the average number of cases as parameter. Also, duration and severity of illness vary for each individual patient. Then, if this population would be studied for a long time, the disease burden would not be constant over the years but would vary. Each variable can be represented by a statistical distribution. A simulation model using Latin Hypercube sampling is implemented in @RISK 4.5 (Palisade Corporation, Newfield, NY, USA) to calculate the distribution of the disease burden. The mean (or median) from this distribution represent the mean (or median) disease burden over a number of years and percentile values can characterise the variability over the years.

For example:
N_u ~ Poisson(1000)
t_u ~Gamma (3.2, 1.75)
w_u ~Beta (1.23, 1.90)

Here, ~ means: is a sample from. The disease burden for one patient is calculated as:

$yld_u = t_u \times w_u$

Then, the disease burden for the total population is

$YLD = \Sigma_{Nu}.\ yld_u$

The graph represents the simulated data if the population would be followed for 100 years and demonstrates the variability in the disability burden.

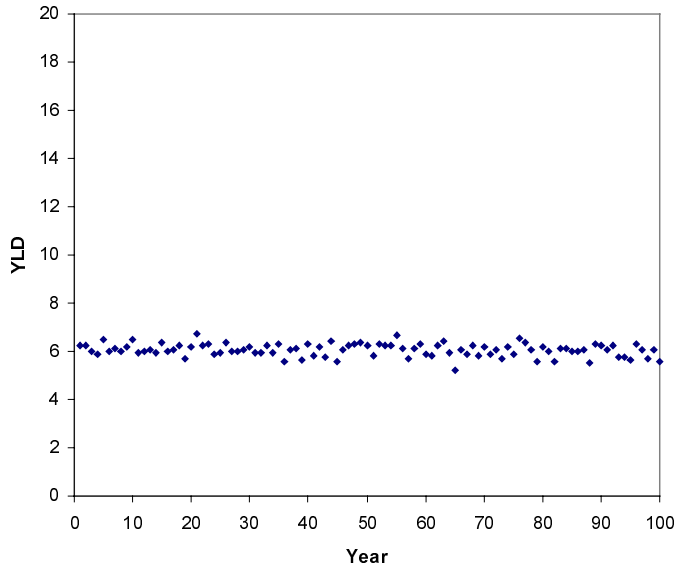

Figure 1. Variability of the disease burden, example B

Table 2.1. Summary statistics for the simulation results of example B

Mean	6.05
Median	6.05
5-percentile	5.76
95-percentile	6.29

The mean of this simulation is not exactly equal to the point estimate in example A (6.03). This is a random effect, due to the small number of iterations in example B.

C. Uncertainty and variability: incidence uncertain, severity and duration variable

In reality, the incidence of illness is not known but is estimated from observational data on a sample of the population. The uncertainty in the incidence rate can also be represented by a statistical distribution. The mean or median of this distribution represents our best estimate of the true incidence rate, whereas the range between e.g. the 5th and 95th percentile represents our uncertainty about the true incidence. Any value that is sampled from this distribution represents one possible value of the true incidence rate, and can be used as an input for a simulation of the variability of the disease burden over years. By repeating this process, using other samples of possible values for the incidence rate, a set of distributions is obtained that each represent one possible variability distribution of the disability burden.

Simulation 1	Simulation 2	…..	Simulation S
N_{u1} = 1000	N_{u2} = 279	…..	N_{uS} = 3058
t_{u1} ~Gamma (3.2, 1.75)	t_{u2} ~Gamma (3.2, 1.75)	…..	t_{uS} ~Gamma (3.2, 1.75)
w_{u1} ~Beta (1.23, 1.90)	w_{u2} ~Beta (1.23, 1.90)	…..	w_{uS} ~Beta (1.23, 1.90)
$yld_{u1} = t_{u1}$ x w_{u1}	$yld_{u2} = t_{u2}$ x w_{u2}	…..	$yld_{uS} = t_{uS}$ x w_{uS}
$YLD_1 = \Sigma_{Nu1}. yld_{u1}$	$YLD_2 = \Sigma_{Nu2}. yld_{u2}$	…..	$YLD_S = \Sigma_{NuS}. yld_{uS}$

The graph represents the results of 10 different simulations of data if the population would be followed for 100 years. Each time series of points represents the variability in the disability burden given a random sample from the uncertainty distribution of the incidence rate.

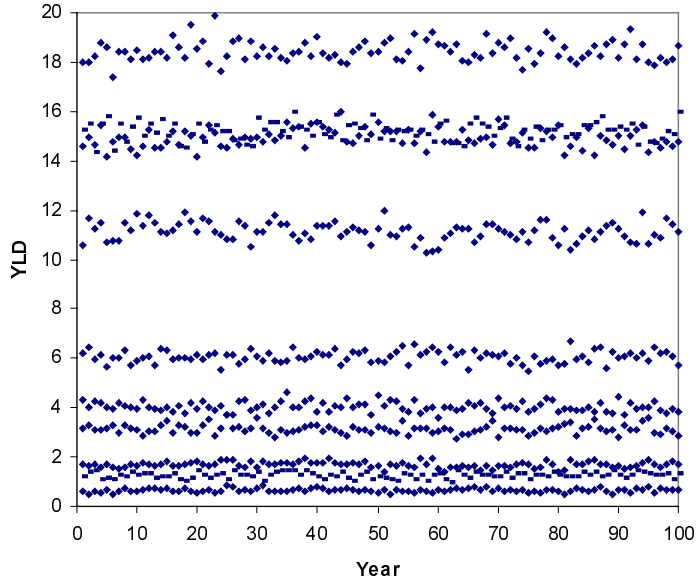

Figure 2. Variability and uncertainty of the disease burden, example C

Table 2.2. Summary statistics for the simulation results of example C

Simulation	1	2	3	4	5	6	7	8	9	10
Incidence	1000	279	666	515	208	2472	1850	107	2518	3058
Mean	6.06	1.69	4.04	3.12	1.26	14.9	11.1	0.65	15.0	18.4
Median	6.08	1.69	4.01	3.12	1.28	14.9	11.1	0.64	15.2	18.3
5-percentile	5.69	1.48	3.74	2.84	1.06	14.3	10.5	0.54	14.5	17.9
95-percentile	6.45	1.89	4.38	3.49	1.45	15.5	11.7	0.78	15.8	19.1

The variability in simulation 1 (range between 5- and 95-percentile) is larger than in example B, whereas a lower value is expected. In example C the incidence is constant, and it is variable in example B. This is a random effect, due to the small number of iterations in both examples.

Presentation of results

A graph of the results, such as in Figure 1 and Figure 2 is only instructive if variability is small compared to uncertainty. If variability is relatively large, the results from each simulation would overlap, and the graph would not be instructive. A more useful way to represent the output data is by a cumulative distribution plot.

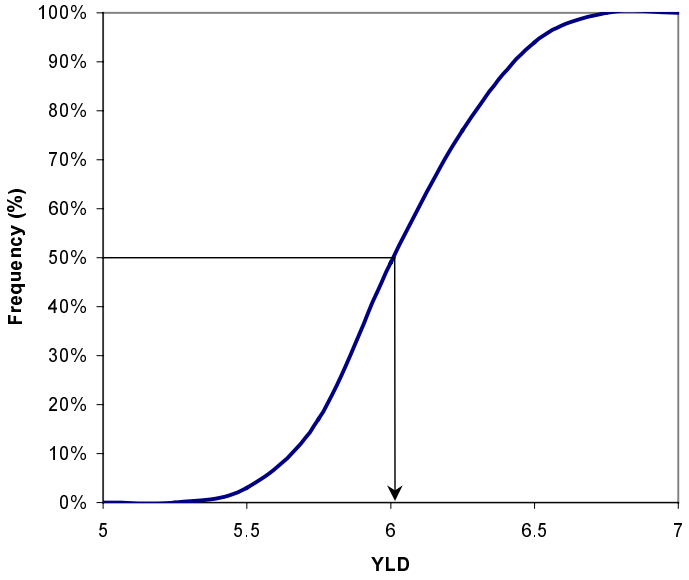

Figure 3. Cumulative distribution plot of example B

Figure 3 shows a cumulative plot of the output of example B. The lines in the graph show the interpretation of this plot. 50% of all output data is less than or equal to the corresponding value on the x-axis. In this way, any percentile, e.g. as reported in Table 2.1 can directly be read from the plot.

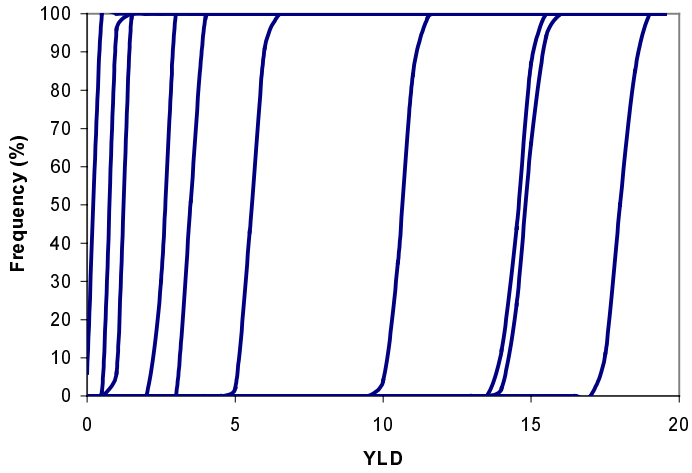

Figure 4. Cumulative distribution plots of example C

Figure 4 shows the cumulative distribution plots of the output of example C. We now have one line for each simulation. In this example, the lines do not overlap, indicating that the effect of variability is small compared to uncertainty. If the relative importance of variability would be larger, the lines would tend to overlap.

3. Epidemiology of infections with Shiga-toxin producing *Escherichia coli* O157 in the Netherlands

3.1 General

Shiga-toxin producing *Escherichia coli* O157 (STEC O157) was first recognised as a human pathogen in 1982, when it was implicated in two outbreaks of diarrhoeal illness associated with consumption of hamburgers. STEC O157 is one of a larger group of *E. coli* strains who have the ability to produce Shiga-like toxins and are commonly designated as STEC. Among STEC, serotype O157, and in particular the flagellar subtype H7 has received most attention because it is the most common serotype with a world-wide distribution, and because it can easily be detected in the laboratory by its inability to ferment sorbitol. Other serotypes are isolated from clinical material, but less frequently [7,8,36]. Large outbreaks of STEC O157 have been identified world-wide, some at an exceptionally large scale. These include:

- 243 patients and 4 deaths in Cabool, Missouri, USA (1990) associated with contaminated drinking water [80];
- 501 patients and 3 deaths in Washington State, USA (1992-3) associated with hamburgers [3];
- 521 patients and 17 deaths in Lanarkshire, Scotland (1996) associated with meat from a butcher shop [19];
- approximately 10,000 schoolchildren, staff and household contacts and 14 deaths in Sakai City, Japan (1996) associated with radish sprouts [81];
- over 1000 cases and two deaths in New York, USA (1999) (including patients with campylobacteriosis) associated with untreated water used for ice and drinks [56];
- over 2300 cases and six deaths in Walkerton, Canada (2000) (including patients with campylobacteriosis) associated with contaminated drinking water [2].

In contrast to these large outbreaks and the associated publicity, the incidence of endemic cases of STEC is relatively low. In the United States [13], active laboratory surveillance in the Foodnet project demonstrates an incidence between 2 and 3 cases per 100,000 inhabitants per year (compare 20-25 for *Campylobacter* and 10-15 for *Salmonella* spp.). In the UK [62], approximately 1000 isolates of STEC O157 are reported per year vs. 50,000-60,000 for *Campylobacter* and 20,000-30,000 for *Salmonella*. Within the UK, the incidence is highest in Scotland with a reported incidence of 6 per 100,000 pyr [70]. In the early nineteen-nineties, the incidence in Alberta, Canada was reported to be as high as 12 per 100,000 pyr [91]. A population-based estimate for the USA [50] is in the order of 30 cases per 100,000 inhabitants per year (compare with 1000 cases of campylobacteriosis per 100,000 pyr). Only one outbreak of STEC O157 associated diarrhoeal illness has been recognised in the Netherlands, involving 5 persons in a single household, possibly associated with transmission from farm animals [42]. Recent studies in the Netherlands, as summarised in this chapter, also indicate a low incidence of endemic cases.

Infections with STEC O157 may be asymptomatic, or may lead to diarrhoeal illness (see Figure 1). In many cases, stools are bloody and accompanied by abdominal cramps, a syndrome also known as haemorrhagic colitis. Fever, chills, nausea and vomiting also frequently occur as a consequence of STEC O157 infection [79].

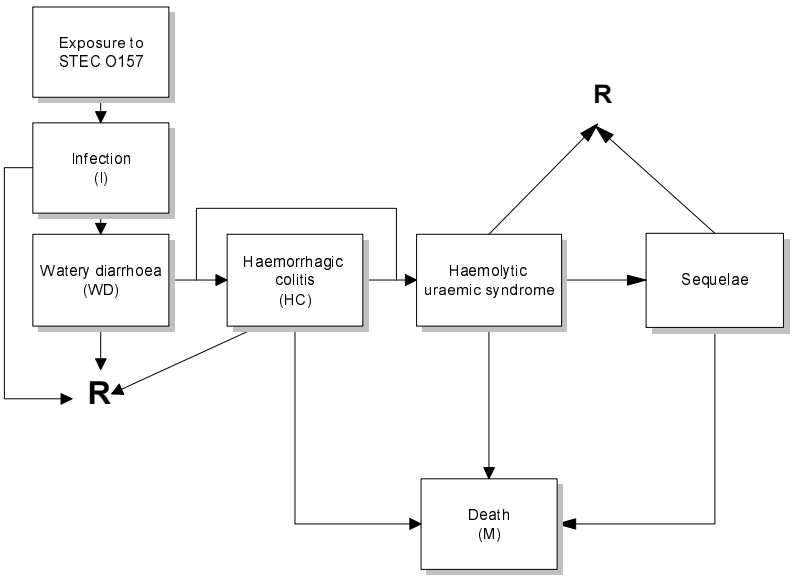

Figure 5. Chain model of outcomes of exposure to STEC O157

(R: recovery)

In 1985, Karmali and colleagues [44] reported an association between STEC and post-diarrhoeal haemolytic uraemic syndrome (D+ HUS), which occurs mainly in young children and may lead to death during the acute phase, to end stage renal disease or other sequelae. Since then, numerous studies, both in endemic and in outbreak situations have demonstrated that STEC, and particularly serotype O157, is the major etiologic agent of D+ HUS. In the Netherlands, similar results have been obtained [14,84]. One outbreak has been identified: a cluster of four children with HUS (two were culture positive for STEC O157) was associated with swimming in a shallow lake [20].
For reviews on the epidemiology and clinical aspects of STEC O157 see [38,41,49,79].

3.2 Acute diarrhoeal disease

3.2.1 Incidence

There are different possibilities for surveillance of gastrointestinal illness including population-based, sentinel (general practice based) and laboratory based surveillance, infectious disease notification, registration of deaths and hospital diagnoses, outbreak investigations and case-control studies of sporadic cases [9]. Each study type samples a different part of the population and has its specific strengths and weaknesses. No single information source is sufficient to get a complete picture of the impact of a specific intestinal pathogen on the health of the population. Combining information from different surveillance studies results in the best possible estimates.

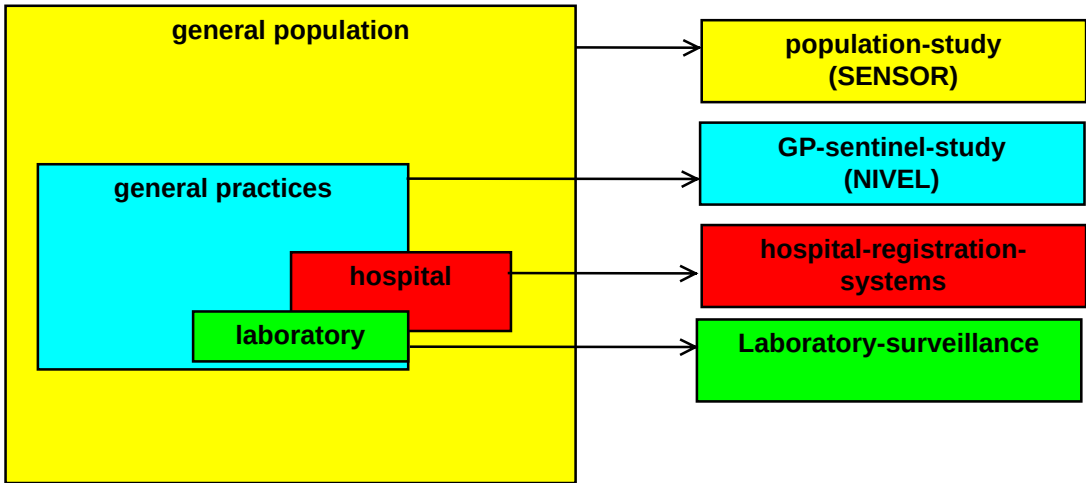

Figure 6. Surveillance of gastroenteritis in the Netherlands, 1996-2000

Information on the incidence of STEC O157 associated gastrointestinal illness in the Netherlands is available from three sources as indicated in Figure 6: population surveillance, GP sentinel surveillance and laboratory surveillance.
SENSOR was a *prospective population-based cohort study* with a nested case-control study and was carried out between December 1998 and December 1999. SENSOR evaluated the incidence of gastroenteritis in the general population in the Netherlands and the associated pathogens. 1050 cases of gastroenteritis[1] were observed in 2229 pyr, or a crude incidence of 471 per 1000 pyr [37]. The age, gender- and cohort standardised incidence was 283 cases per 1000 pyr [23]. In a nested case-control study, 699 faecal samples from individuals with gastro-enteritis were analysed for STEC, with two positive results. Neither of the isolated STEC strains was serotype O157. On the basis of these data, it is not possible to make a direct estimate of the incidence of STEC O157 associated gastrointestinal illness in the Dutch general population (see Appendix 1A). An alternative estimate for the incidence in the total population can be based on the incidence of consultations of a general practitioner, multiplied by a factor to account for cases, who do not seek medical attention.

Sentinel surveillance in general practices
GP sentinel surveillance using the established NIVEL system identified 2553 cases of GP consultation for gastroenteritis[2] in 320,227 pyr or 8 per 1000 pyr (age standardised and partially adjusted for incomplete participation of cases and GPs, and for list inflation) [19]. In a nested case-control study, 798 faecal samples from patients with gastroenteritis were analysed for STEC, with 4 positive results. One of the STEC strains was *E. coli* O157 K- H-. In a further study [24], the degree of underreporting in the NIVEL GP sentinel study was evaluated by comparison with SENSOR data obtained in the same population and in the same period. Direct enumeration of GP visits, reported by patients in the SENSOR study resulted in a standardised incidence of 13.8 per 1000 pyr. Only 17% of all patients who reported

[1] Case definition: at least three loose stools in 24 hours or at least three times vomiting in 24 hours, or diarrhoea with two or more additional symptoms or vomiting with two or more additional symptoms in 24 hours. Additional symptoms could be diarrhoea, vomiting, abdominal cramps, abdominal pain, fever, nausea, blood in stool, or mucus in stool. After a case episode, a two-week symptom free period was taken into account before a participant could become a case again.
[2] Case definition: three or more loose stools in 24 hours; or diarrhoea with two additional gastrointestinal symptoms (vomiting, nausea, fever, abdominal cramps, abdominal pain, blood in stool, mucus in stool) or vomiting with two additional gastrointestinal symptoms (diarrhoea, nausea, fever, abdominal cramps, abdominal pain, blood in stool, mucus in stool) preceded by a symptom-free period of 2 weeks.

having consulted their GP were actually reported by the GPs in the NIVEL study. Applying this correction factor to the NIVEL data (adjusted for list inflation), results in an estimate of 35 consultations per 1000 pyr. Most probably, the true consultation rate for all cases of gastroenteritis is between these extremes. GPs were more likely to include a patient in the NIVEL case-control study if gastrointestinal complaints were chronic, or were more severe and of longer duration. Because STEC O157 is a relatively severe form of gastroenteritis with relatively long duration, it is likely that the degree of underreporting is lower than for all gastroenteritis cases. We will therefore use the incidence estimate of 13.8 consultations for gastroenteritis per 1000 pyr in the base-case, and will present other estimates in a sensitivity analysis.
From the data presented in this section, a median incidence of 182 (90% credible interval 12 - 859) GP consultations for STEC O157 associated gastroenteritis per year can be calculated (13.8/1000 pyr x 15.8 x 10^6 persons x 1/798 STEC O157). The uncertainty is quantified by Bayesian statistics, as described in Appendix 1B. Results are shown in Figure 7 and Table 3.1.

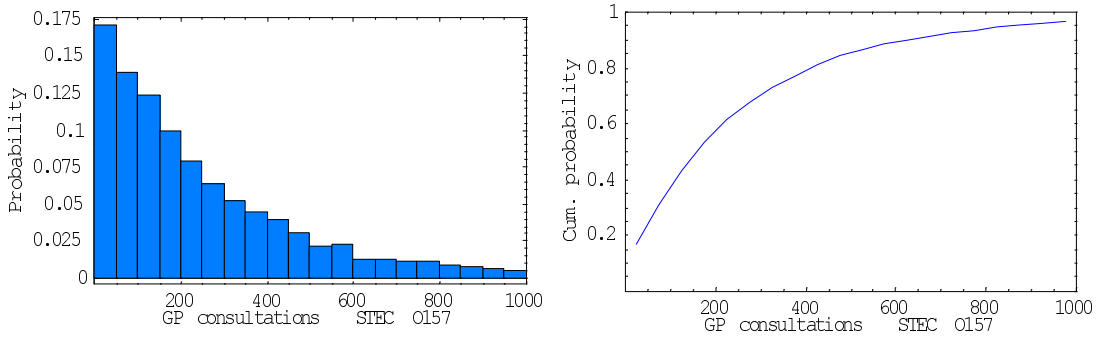

Figure 7. Uncertainty of incidence of GP consultations as a result of STEC O157 associated gastroenteritis (left histogram, right cumulative frequency distribution)

Consultation of general practitioners by cases in the general population
To estimate the proportion of all cases in the population who consult their GP, we have to account for the high severity of STEC O157 associated gastroenteritis. One of the most distinguishing factors is the frequent occurrence of bloody diarrhoea. Michel *et al*. [52] report a literature survey on selection mechanisms in identifying cases of *STEC* O157 associated illness by different surveillance systems, and apply the data to an estimate of the under-reporting rate in Ontario, Canada. Using the approach of Michel *et al*. in a Bayesian framework, and including Dutch data on GP consultation for bloody and non-bloody diarrhoea [19], we estimate that 14% (median, 90% credible interval 7 - 27%) of all cases with STEC O157 associated gastroenteritis report to their GP (see Appendix 1C). In a GP practice, only a very small proportion (median 0.09%, 90% credible interval 0.006 - 0.37%) of all gastroenteritis cases is due to STEC O157.

Incidence of STEC O157 associated gastroenteritis in the general population
Combining the information on GP consultations and the fraction of cases who actually do so, we estimate the median incidence of STEC O157 associated gastroenteritis in the general population as 1251 (90% confidence interval 83 - 2620) cases per year. The uncertainty in this estimate (Appendix 1C) is shown in Figure 8 and in Table 3.1. In the simulation model, it is possible to reconstruct the case-control study as carried out in SENSOR (see Appendix 1D). The results indicate that, under the assumptions and input data of the baseline model,

there is an 85% probability of not detecting a single case associated with STEC O157. Hence, the baseline model is not incompatible with the observations in SENSOR.

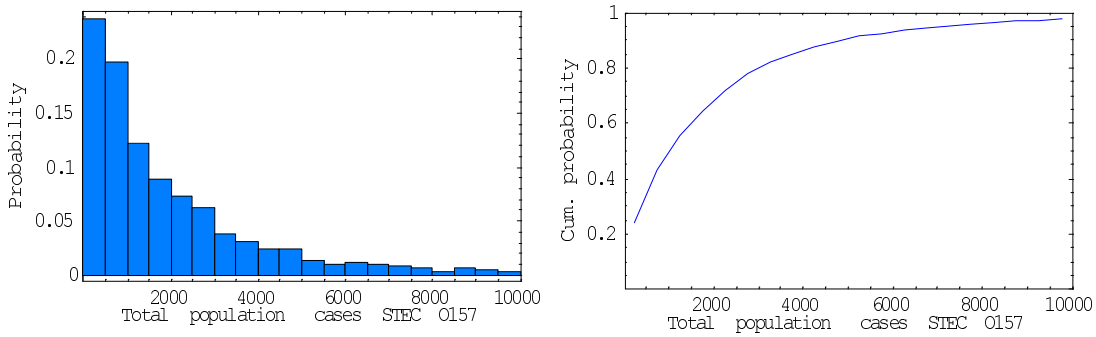

Figure 8. Uncertainty of incidence of total population cases of STEC O157 associated gastroenteritis (left histogram, right cumulative frequency distribution)

Table 3.1. Output distributions of incidence estimates of STEC O157 associated gastroenteritis

Parameter	5-perc.	Median	Mean	95-perc.	St. dev.
GP consultations STEC O157 (per year)	12	182	274	859	294
Total population cases STEC O157 (per year)	83	1251	2111	7157	2620
Aetiologic fraction GP STEC O157 (%)	0.006	0.09	0.13	0.37	0.13
Fraction of STEC O157 patients reporting to GP (%)	7.0	14.3	15.4	27.3	6.3

Nature of diarrhoeal symptoms and asymptomatic infections

Most reviews on STEC O157 associated gastrointestinal illness report that a high proportion of patients suffers from bloody diarrhoea. In contrast, in most outbreaks a sizeable proportion of cases manifests itself with non-bloody diarrhoea. This apparent difference may be due to the fact that clinical aspects in most reviews are based on reports from laboratory-confirmed cases, which are positively selected for bloody stools. To get an estimate of the proportion of bloody and non-bloody cases in the population, outbreak data are the more pertinent source of information. Michel *et al*. [52] have reviewed the literature and summarise data from 10 outbreaks. The data do not suggest that there are differences between population groups, i.e. based on age. We use an overall estimate of 48.3% (253/538) of symptomatic patients who will develop bloody diarrhoea.

Asymptomatic infections are not recorded in symptom-based surveys, but an estimate of the proportion of infected persons who do not show symptoms can also be obtained from outbreak investigations, in which faecal specimens from the total population at risk was cultured. Michel *et al*. [52] give a summary of such outbreaks reported in the literature. The data do not indicate that the proportion of asymptomatic cases differ among the various populations involved in these outbreaks. Hence, we use an overall estimate, based on 50 asymptomatic carriers among 279 culture-positive persons. Table 3.2 combines this

information with the estimates for symptomatic cases as reported above. Annually, there are approximately (median values) 1540 infections with STEC O157, of which 270 are symptomless. Of the 1250 symptomatic cases, 590 have bloody diarrhoea and 670 have non-bloody diarrhoea. Note that the medians do not exactly add up because the distributions are very skewed.

Table 3.2. Output distributions of incidence estimates of outcomes of STEC O157 infection

Parameter	5-perc.	Median	Mean	95-perc.	St. dev.
Total population cases STEC O157 (per year), of which	83	1251	2111	7157	2620
Bloody diarrhoea	39	590	992	3355	1230
Non-bloody diarrhoea	43	667	1120	3755	1394
Asymptomatic infections (per year)	18	269	464	1589	580
Total infections (per year)	103	1538	2574	8804	3192

Age distribution

Laboratory surveillance was intensified in 1999, when all medical microbiological laboratories were requested to report all positive findings of STEC O157 to the Regional Health Services, and to submit an isolate for typing to RIVM [85,86]. In 1999, 36 patients with O157 STEC infection were identified, or 0.2 cases per 100 000 pyr. The number of cases in laboratory surveillance is sufficient to get information about age-distribution, see Table 3.3. This information will also be used to infer the age distribution of cases in the general population, assuming that there is no age-related selection bias in submission of stool specimens to clinical laboratories. In general, this assumption is not valid for gastrointestinal illness because there is a higher tendency to consult a general practitioner and to submit a faecal specimen if the illness occurs in children [24]. However, STEC O157 frequently results in bloody diarrhoea, which is another determinant of consultation and faecal examination, thereby reducing the age-related selection bias. Among the 36 patients were at least 6 HUS patients (this information was not available for 18 patients). Of the HUS patients, 4 were in the age group 0-4 yr and 2 in the 15+ group. Because it is likely that at least one stool culture will be obtained for each HUS patient, this may result in a bias towards inclusion of a larger percentage of young children.

Table 3.3. Age distribution of cases of STEC O157 associated gastroenteritis identified by laboratory surveillance

Age class	Number of cases	Proportion of cases	Uncertainty (90% CI)[1]
0-4	9	0.25	0.14-0.37
5-14	6	0.17	0.08-0.28
15+	21	0.58	0.44-0.72
Total	36	1.00	

[1] See Appendix 1

Combining the above data for bloody/non-bloody diarrhoea, symptomatic cases, age-distribution and incidence of diarrhoeal cases leads to the summary as shown in Table 3.4 (methods in Appendix 1D).

Table 3.4. Age-distribution of symptomatic cases and asymptomatic infections by STEC O157 in the Netherlands (median values)

Age class	Symptomatic cases			Asymptomatic infections	Total infections
	Total cases	Bloody	Non-bloody		
0-4	300	140	158	64	365
5-14	188	90	99	41	230
15+	720	338	380	156	878
All ages	1251	590	667	269	1538

3.2.2 Duration of gastroenteritis

Several outbreak studies have demonstrated that the duration of bloody diarrhoea is longer than of non-bloody diarrhoea [4,77,80]. We base our estimates on the report by Belongia *et al*. [4], who investigated a hamburger-associated outbreak in the USA, affecting students at a junior high school (age 9-15 years). These authors report a median duration of 5 resp 3 days with ranges of 2-12 resp 1-7 days for bloody and non-bloody diarrhoea. Swerdlow *et al*. [80] reports lower values in a waterborne outbreak, affecting all members of the community (means 4.6 resp. 3.7 days). We use Gamma distributions to describe the variability in the duration, see paragraph 4.2.1. These distributions have means of 5.6 resp 3.4 days. Spika *et al*. [77] report higher values in an outbreak in a day-care centre (12.2 resp 6.8 days). These data may be taken as an indication of increasing duration at younger ages, but the available data were too scarce to take this effect explicitly into account.

3.2.3 Mortality

STEC O157 associated mortality by causes other than HUS is rare and only very large outbreaks will give some information. In the Walkerton outbreak [2], 1 fatal case was recorded among 2321 patient. Applying this estimate to the above mentioned number of cases in the Netherlands would lead to a predicted mean of 0.66 deaths per year (2 per 3 years). Laboratory surveillance is another source of information. Among 120 cases recorded in the Netherlands in 1999-2001, one death in a child was due to HUS and 1 death in a woman aged 85 years was attributed to the consequences of diarrhoeal illness. We base our estimate of the case-fatality ratio on this single case, and include the uncertainty as described in Appendix 1. The low number of recognised fatal cases implies that there is no accurate information on age-distribution. We assume that the age distribution is similar as for all cases of gastro-enteritis and use data from Statistics Netherlands, as previously reported [39]. Data and uncertainty analysis are shown in Appendix 1G.

3.3 Haemolytic uraemic syndrome

3.3.1 HUS and TTP

Haemolytic Uraemic Syndrome (HUS) is a serious complication of STEC O157 associated gastro-enteritis that occurs mainly in young children following an episode of (bloody) diarrhoea. HUS is clinically defined by the triad microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure. Thrombotic thrombocytopenic purpura (TTP) is a clinically related condition that occurs more frequently in adults and is more frequently associated with a familial history. The diagnostic criteria of TTP are the same as of HUS, but HUS occurs more frequently in children whereas TTP occurs more frequently in adults. TTP is additionally characterised by fever and neurological dysfunction, and symptoms of renal failure are less prominent. However, atypical and incomplete cases of HUS and TTP do occur and HUS patients may also develop fever or neurological involvement. Therefore, the two conditions are often regarded as variants of a single syndrome, collectively described as

thrombotic microangiopathy. HUS is strongly associated with STEC, and a relationship of TTP with this group of bacteria is also suggested in the literature [46,79] but other authors considered TTP associated with STEC O157 the same disorder as HUS [49]. Recent work by Furlan and colleagues [31,32] identified an additional mechanism that is involved in development of TTP. Nonfamilial TTP is due to an inhibitor of von Willebrand factor-cleaving protease that is identified as an IgG antibody. The familial form appears to be caused by a constitutional deficiency of the protease. In both cases, unusually large multimers of vWF circulate in the bloodstream, and may cause platelet aggregation under high shear stress such as encountered in the microvasculature. Patients with HUS do not have a reduced activity of vWF cleaving protease. Instead, exotoxin induced endothelial damage in the renal glomeruli seems to induce the release of large multimers of vWF from intracellular pools, thus leading to localised platelet agglutination. In this study we will only use the descriptive term HUS for renal complications of infection with STEC O157. Cases reported in the literature as TTP (mainly in adults) will also be classified as HUS.

3.3.2 Incidence of HUS in the Netherlands and fraction attributable to STEC O157

In the Netherlands, the incidence of HUS is 2.0 per 100 000 children younger than 5 years [83], i.e. 20 cases per year[3]. HUS does occur in children of 5 years and above, but less frequently. The age distribution in Table 3.5 indicates that 1 case of HUS in the 5-14 year old is expected for 8.2 cases in the 0-4 year old. Hence, the incidence of HUS in children under 15 is $20 + 20/8.2 \approx 22$ cases per year. The incidence at ages above 15 is estimated indirectly from laboratory surveillance data. Among 120 cases in 1999-2001, there were 18 HUS patients. Of these, 13 (72%) were less than 15 years of age, five were older (17, 17, 22, 45 and 70 years). Combining these data leads to an average incidence of 30 cases of HUS per year (all causes).

Van de Kar *et al*. [84] found evidence for STEC infection in 88/113 paediatric HUS cases and 2/65 controls, attributable proportion 77%. Different methods were used to establish this relationship: isolation of STEC O157 from faeces, detection of ST in faeces or in polymyxin B extracts of colony sweeps and serology for VT-neutralising or anti O157 antibodies. Hence, in some cases with evidence for STEC infection, another serovar than O157 may have been involved. However, the majority of cases were associated with serovar O157 as is evidenced by serum antibodies against O157 antigen in 71 out of 88 positive cases. Using this result as an estimate of the lower limit of cases attributable to STEC O157, the minimum attributable proportion is 62%.

[3] In 1999 and 2000, a telephone enquiry among academic paediatric nephrology units in the Netherlands by prof. L.A. Monnens (University Hospital Nijmegen, Department of Paediatrics) resulted in a total of 19 cases per year. Hence, the incidence appears to be relatively constant throughout the years.

Table 3.5. Age distribution of HUS patients admitted to the Pediatric Nephrology department of University Hospital Nijmegen, 1974-1993 [14]

Age (mid-point)	Number of cases
0.5	17
1.5	29
2.5	21
3.5	15
4.5	9
5.5	6
6.5	1
7.5	1
8.5	4
9.5	5
10.5	1
11.5	3
12.5	1

3.3.3 Clinical aspects of HUS

Siegler [71,72] reviews the clinical features of D+ HUS, see Figure 9. Acute renal failure is the most prominent feature, leading to oliguria or anuria in the majority of patients. Hypertension occurs in the majority of cases but often resolves in time. The brain is also frequently affected with evidence of central nervous system (CNS) dysfunction in about one third of patients. This may lead to alterations of conciousness (including coma) and seizures. Stroke or cerebral oedema is present in 3-5% of children. Thrombotic microangiopathy in the pancreas may lead to pancreatitis, diabetes mellitus or exocrine dysfunction. Transient hepatocellular damage occurs in approximately 40% of cases, whereas other organs (heart, lungs, muscles, skin, and parotid gland) are less frequently involved. Therapy is mainly based on supportive care, with meticulous attention for fluid and electrolyte balance and treatment of hypertension. Patients are routinely treated with peritoneal dialysis or haemodialysis. The duration of hospitalisation for D+ HUS patients is in general 2-4 weeks (N. van de Kar, unpublished data.).

3.3.4 Mortality associated with HUS

Due to earlier recognition and improved management in the acute phase of the disease, the mortality associated with paediatric cases of D+ HUS has decreased to less than 5%. Appendix 3 presents a summary of the literature, which results in a pooled estimate of the case fatality ratio of 3.7 %. On the basis of limited data, we assume that this low case-fatality ratio is valid for cases up to 65 years of age. At higher ages, we estimate a considerably higher case-fatality ratio of 56%, based on Scottish outbreak data [27]. The late fatalities that are reported in some papers are accounted for in this study as mortality associated with End Stage Renal Disease (see paragraph 3.3.5).

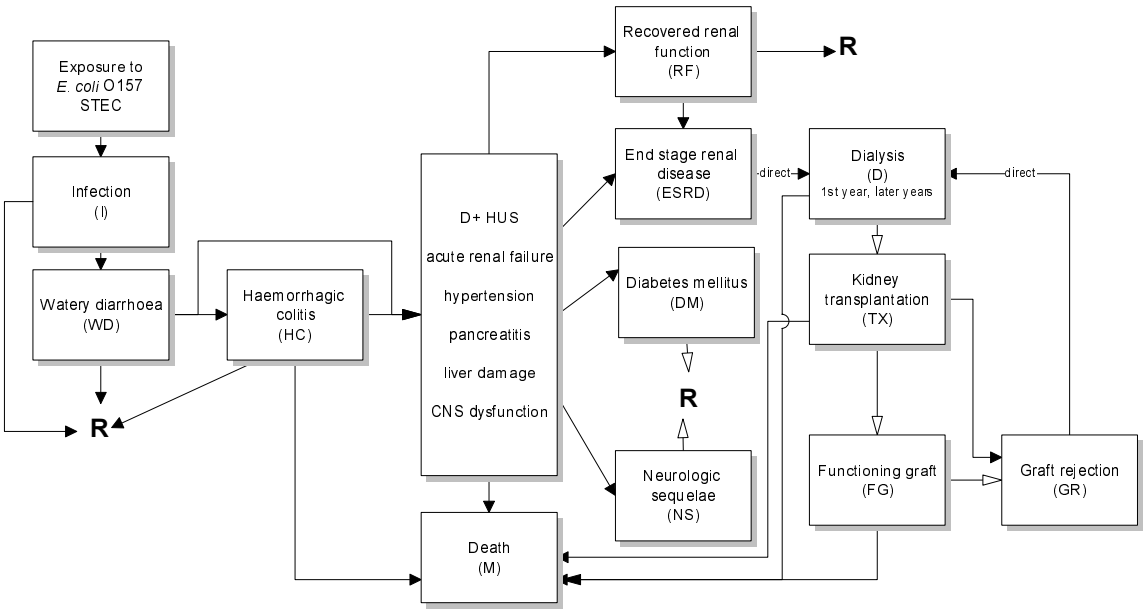

Figure 9. Chain model of outcomes of exposure to STEC O157 including sequelae of HUS (R: recovery)

3.3.5 End stage renal disease

Probability of End Stage Renal Disease

End stage renal disease (ESRD) is one of the serious outcomes associated with HUS [72]. Some patients develop ESRD directly, but renal damage may also become manifest after a period of apparently normal kidney function (late ESRD). Appendix 3 presents a summary of the literature, which results in pooled estimates of the probability of developing direct ESRD of 2.9 %. Here, direct ESRD is defined as a direct outcome of HUS, without recovery of the renal function. The probability of late ESRD (with temporary recovery of renal function) is estimated at 2.3 % in the first 10 years. Indirect information on the probability of late ESRD can be obtained from the observations by Eijgenraam *et al*. [28]. In the period 1969-1986, four paediatric centres in the Netherlands and Belgium identified 11 children who developed ESRD immediately following the acute phase of HUS, and 9 children who developed ESRD 0.5 to 13.2 years later. In other words, cumulated over a period of approximately 10 years, the probability of developing late ESRD is somewhat lower than the probability of directly developing ESRD, which fits well with the above estimates. However, from the long-term follow-up studies performed in Paris, France, it appears that hazard of developing ESRD after initial recovery of renal function may well extend over a period of more than 20 years [33]. Based on this study, we estimate the probability of late ESRD as 8/76 (10.5%), with onset uniformly distributed between 0 and 40 years after D+ HUS. Before the diagnosis ESRD is made, the renal function of these patients will gradually decrease as may initially be evident from reduced glomerular filtration rates, leading to advanced and chronic renal failure. Obviously, these symptoms do affect the quality of life of the patients. Most information in the literature is on paediatric cases, there are only limited data on the clinical course of adult patients and if available, they usually refer to HUS and TTP patients together. We assume that the clinical course in adults is similar to that in children. Some supporting information can be found in Siegler *et al*. [74] who report that the outcome for adolescents (12 - 17 years) is similar to that of younger children. Conlon *et al*. [18] report that of their 51 surviving

patients, 2 (3.9%) required long-term dialysis. No long-term follow-up for adult patients has been reported.

Renal replacement therapy

Patients with ESRD are initially treated with one of different forms of dialysis (D) and may later be eligible for kidney transplantation (TX). The clinical history of ESRD patients was derived from the Renine[4] database. This database records data from all Dutch dialysis and/or transplantation centres on patients who are treated for chronic, terminal renal failure. From the database, information was extracted on 31 new patients, starting with dialysis in the period 1980 to 2000 inclusive with primary diagnosis Haemolytic Uraemic Syndrome (including Moschowitz Syndrome, an older term for TTP), who were less than 16 years of age at the start of treatment. This relatively small number of patients would lead to large uncertainties in parameter estimates. Therefore, data on 75 patients with primary diagnosis pyelonephritis were included in the analysis, because they were expected to have similar prognoses (L.A.H. Monnens, personal communication). The validity of this hypothesis was confirmed by statistical analysis. In total, data on waiting time to transplantation were available for 2348 patients and data on time to graft failure for 1006 patients (see Table 8).

Table 3.6. Age distribution of patients in the Renine database, by diagnosis and outcome

Age class	**Time to tranplantation**		**Time to graft failure**	
	HUS	PYN	HUS	PYN
0-15	31*	75	21	76
16-44	88	631	51	527
45-64	35	779	12	301
65-74	7	522	0	18
75+	5	175	0	0
Total	166	2182	84	922

* Number of patients available for analysis

The results of the survival analysis are summarised in Table 3.7, details can be found in Appendix 4. For time to transplantation, there was no significant difference between patients with HUS and PYN in any of the age classes. For the 75+ age class, only censored data were available, and these patients were included in the 65+ age class. The median time to transplantation increases with age and there is considerable variability. At higher ages, waiting times can be so long that patients are no longer eligible for transplantation. In the 0-15 year old, the probability of being transplanted increases significantly with longer waiting times. This may be due to the availability of living-related donors, who will donate a kidney when a child is on the waiting list for a longer period of time.

For time to graft failure, there were significant differences between HUS and PYN patients, and analyses were carried out for HUS patients alone. There were no significant differences between age groups. The median duration of life with a functioning graft was 4 years, but this is highly variable between patients. Directly after transplantation, there is a high probability of graft rejection, but this probability decreases strongly with time. This results in the 90% credible interval for the time to graft failure to range from 0.016 years (6 days) to 96 years (effectively lifelong).

[4] Renine, Renal Replacement Registry of the Netherlands, Rotterdam, the Netherlands

Table 3.7. Time to transplantation and time to graft failure by age group

Age class	Time to transplantation (HUS and PYN)		Time to graft failure (HUS only)	
	median (yr)	90% CI	median (yr)	90% CI
0-15	1.7	0.2-5.3		
16-44	2.5	0.2-9.6	4	0.016-96
45-64	6.7	0.5-30		
65+	70	5-250		

The Renine database also allows for analysis of case-fatality ratio's in dialysis patients and after renal transplantation. In the first year after starting dialysis, mortality ratio's are relatively high and different between age groups, see Table 3.8. There were only few fatalities after renal transplantation, and no information on age-specific risks could be obtained.

Table 3.8. Case-fatality ratio's in the first year after starting dialysis and after renal transplantation

Age class	Case-fatality ratio	
	dialysis	renal transplantation
0-15	5%	
16-44	9%	8%
45-64	37%	
65+	79%	

3.3.6 Non-renal sequelae

Siegler [71] reviews the extrarenal involvement associated with D+ HUS. Most frequently (*i.e.* in more than 5% of cases) are gastrointestinal or rectal prolapse (8-10%), pancreatitis (20%), diabetes mellitus (8%), liver damage (40%), and central nervous system involvement (seizures 20%, coma/semicoma/stupor 15%). In many patients, the effects are transient or mild, but diabetes mellitus and neurologic symptoms may persist after recovery from HUS. Nevertheless, prognosis is remarkably good, even for children who have suffered convulsions in the acute phase of the disease. Given the limited duration and/or severity of the non-renal sequelae, their contribution to the overall disease burden is small and will not be further evaluated. For the individual patient, however, these sequelae may be very important. Colonic necrosis or gangrene may necessitate complete or partial colectomy. Brandt *et al.* [10] report that four of 37 young HUS patients in the 1993 Washington State outbreak required colectomy (three total, one subtotal). Of these, two died; two survived of which one with and one without renal impairment. These authors also report that at follow-up of 29 patients after 2-3 years, three developed symptomatic cholethiasis 1-3 years after HUS, and all required cholecystectomy. Because all 6 cases lost to follow-up suffered from mild disease, the best denominator is all 35 survivors. So there were three cases of cholecystectomy in 35 patients (6%).

3.4 Summary of incidence data

Table 3.9 gives a summary of incidence data as described in this chapter. From these data, it is possible to infer that the probability of developing HUS after STEC O157 associated gastroenteritis is 4% in the 0-4 yr age group, 1.6% in the 5-14 yr age group and 0.8% for ages above 15. These probabilities are considerably smaller than those reported in outbreak

investigations, see Figure 10. This may be related to incomplete case assurance in outbreak studies. Frequently, bloody diarrhoea is an important component of case-definitions in STEC O157 outbreak investigations, which results in missing a considerable proportion of non-bloody cases. However, the probability of HUS given bloody diarrhoea in our study is also at the low end of estimates from outbreak studies. Other sources of under-ascertainment may (partly) explain this difference. It is also possible that outbreak strains are more virulent than strains involved in endemic cases, or that our incidence estimates for STEC O157 associated gastroenteritis are too high.

Table 3.9. Summary of incidence estimates for gastroenteritis and D+ HUS in the Netherlands

Age group	**0-4 yr**	**5-14 yr**	**15+ yr**	**Total**
Gastroenteritis				
All cases	300	188	720	1251
Bloody diarrhoea	140	90	338	590
Mortality	NA[3]	NA	NA	0.56
D+ HUS				
Clinical	12	3	6	21
$\pi_{H\|G,S}$[1]	0.04	0.016	0.008	0.017
$\pi_{H\|B,S}$[2]	0.086	0.033	0.018	0.036

[1]Probability of developing HUS as a consequence of STEC O157 associated gastroenteritis (all cases)
[2]Probability of developing HUS as a consequence of STEC O157 associated bloody diarrhoea
[3]NA: not available

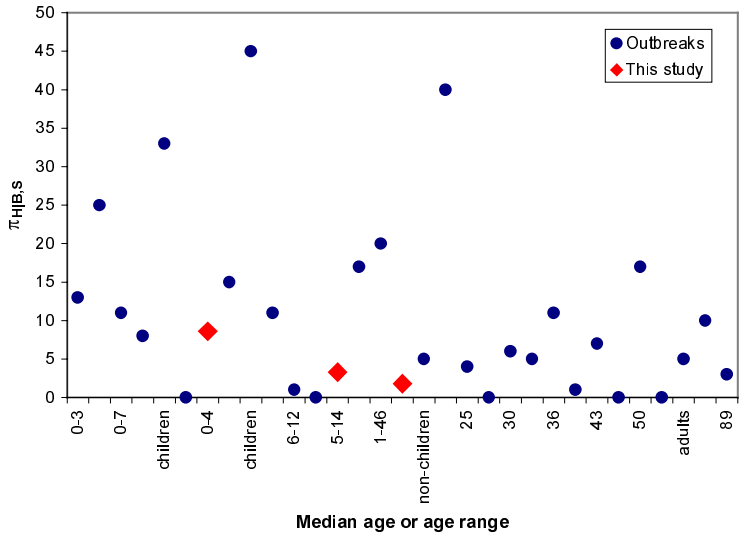

Figure 10. Probability of developing HUS in relation to the age of patients: comparison of outbreak reports and estimates from this study (data see Table 3.9 and Appendix 2)

4. Disease burden of infections with Shiga-toxin producing *Escherichia coli* O157

4.1 Severity weights

A preliminary analysis of the data indicated that for STEC O157, the disease burden is mainly determined by life years lost due to HUS-related mortality. Therefore, the sensitivity of the outcome for severity weights is limited, and no attempts have been made to produce specific estimates for this study. We have chosen the most appropriate weights from published work.

4.1.1 Gastroenteritis

In a previous study on the disease burden of infections with thermophilic *Campylobacter* spp. [39], two severity weights were used for gastroenteritis. The weight for watery diarrhoea (five episodes per day without major pain or cramps) was based on the Global Burden of Disease study [54]. We use a Beta (1.5, 21) distributed weight with median 0.054 and mean 0.066 for non-bloody diarrhoea by STEC O157 to describe the variability of severity per case. A more severe case definition was developed for bacterial gastroenteritis. We use this Beta (1.23, 1.90) distributed weight with median 0.37 and mean 0.39 for bloody diarrhoea. As in the previous study, these weights are applied to the period of acute disease and not on annual profiles, as was done in the Public Health Status and Forecast study [67].

4.1.2 HUS and renal replacement therapy

There are no published severity weights for HUS. We therefore based our estimates on expert opinion, using the Euroqol-5D instrument as described in Appendix 5. The EQ-5D describes the quality of life in five domains (mobility, self-care, usual activity, pain / discomfort, anxiety / depression) on a three point scale (no, some or severe problems). Hence, there are 3^5 = 243 possible health states. Dolan [26] has published a regression model that allows translation of these descriptive health states into a single indicator for quality of life. The mean severity weight for the clinical phase of HUS was 0.90 (range 0.73 - 1.00). After discharge from the hospital, quality of life was not affected, except for patients who developed ESRD.

For ESRD patients, different dialysis modalities are available, including home haemodialysis (HHD), limited care haemodialysis (LCHD), full care haemodialysis (CHD), continuous ambulatory peritoneal dialysis (CAPD) or with automated exchange of dialysis fluid at night (CCPD) [22]. For the purpose of this study, these different options will not be explicitly differentiated. Any patient on dialysis will be assumed to have a probability of being on a specific treatment which is equivalent to the actual situation in the Netherlands in 1993-1996, using data from the study of De Wit *et al*. [22]. These authors evaluated the health status of 165 dialysis patients in the Netherlands, of which 135 participated in the NECOSAD study, a clinical study on the adequacy of dialysis. The latter group is considered representative for the total population of Dutch dialysis patients. The quality of life of these patients was evaluated by different means, including the Euroqol-5D instrument [12]. The Euroqol-5D scores were converted into severity weights as described in Appendix 5, resulting in a mean weight of 0.17 (range 0.00 - 0.68).

Patients who develop late ESRD will experience a gradual loss of kidney function that will affect their quality of life before they become dependent of dialysis. We assumed that in the period between recovery of renal function and commencement of dialysis treatment, the decreasing quality of life follows a linear trend.

Patients on dialysis are eligible for renal transplantation (TX). The severity weight for the TX stage also includes the first year after the surgery. If the graft is not rejected within that year it is assumed to have a normal function, albeit with a finite probability of rejection in following years. The average severity weight for renal transplantation (first year) as based on data from a German study [37] was 0.18, see Appendix 5. The same study provided information on the average severity weight for life with a functioning graft as 0.12.

4.2 Simulation model

The model is set up as a second order Monte Carlo simulation, see Figure 11.

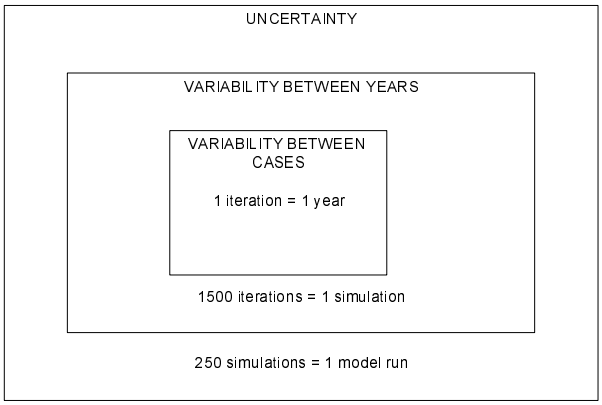

Figure 11. Structure of the simulation model

One iteration of the model represents one year, in which a particular number of cases of gastroenteritis and HUS occur. For each patient, the severity and duration of the illness is simulated, as well as possible complications (mortality, end-stage renal disease). These outcomes are variable between cases. 1500 iterations of the model represent one simulation, that represents the variability between different years. For each simulation, a random sample is obtained from all distributions of uncertain parameters. Thus, running the model for 250 simulations represents the effects of parameter uncertainty on the results. For analysis of other sources of uncertainty, see Chapter 4.5.

4.2.1 Gastroenteritis model

A stepwise summary of the GE model is given on page 33, parameter values are shown in Table 4.1. In each iteration, a Poisson distribution represents the variability in the annual number of cases of gastroenteritis (bloody and non-bloody diarrhoea), with the incidence rate based on estimates in Chapter 3.2.1. The disease burden for all cases of gastroenteritis is then simulated from a distribution representing the total population.
Mortality estimates are based on cases identified in laboratory surveillance. A Poisson distribution represents the variability in reported cases, and the number of fatal cases is sampled from a binomial process. For each individual fatal case, the expected life span at the time of death is sampled. Finally, the disease burden related to gastroenteritis is calculated by accumulation of yld and yll over all cases and all diseases in a year.
One simulation is completed by repeating this iterative process 1500 times, and a model run is based on 250 simulations, each using different random samples from distributions of all uncertain parameters.

i.	Simulate the incidence of bloody diarrhoea	$N_B \sim Poisson(\nu_B)$
ii.	Simulate the incidence of non-bloody diarrhoea	$N_W \sim Poisson(\nu_W)$
iii.	Simulate disease burden of bloody diarrhoea	$yld_B = Gamma\ (N_B \times 1.232, 1.792)/365$[5]
iv.	Simulate disease burden of non-bloody diarrhoea	$yld_W = Gamma\ (N_W \times 1.065, 0.211)/365$
v.	Simulate incidence of laboratory confirmed cases	$N_{S,LS} \sim Poisson(\upsilon_{S,LS})$
vi.	Simulate incidence of mortality	$N_{M,S} = Binomial(N_{S,LS}, \pi_{M,S,LS})$
vii.	Simulate expected life-span of each fatal case	$lyl_G \sim e_{M,G}$
viii.	Calculate disease burden for one iteration:	$daly = yld_B + yld_W + \Sigma\, lyl_G$
ix.	Repeat a and b 1500 iterations = 1 simulation	
x.	Repeat simulation 250 times with random samples from uncertain parameters	

Table 4.1. Parameters of the gastroenteritis model

	Description	Unit	Type[1]	Distribution	Mean	5-perc.	Median	95-perc.
ν_B	Incidence rate bloody diarrhoea	$year^{-1}$	U	Simulation (see 3.2.1)	992	39	590	3335
ν_W	Incidence rate non-bloody diarrhoea	$year^{-1}$	U	Simulation (see 3.2.1)	1120	43	667	3755
t_B	Duration of bloody diarrhoea	day	V	Gamma(3.2,1.75)	5.6	1.6	5.0	11.5
t_W	Duration of non-bloody diarrhoea	day	V	Gamma(2.8, 1.2)	3.4	0.9	3.0	7.2
w_B	Severity of bloody diarrhoea	-	V	Beta(1.23,1.9)	0.39	0.05	0.37	0.82
w_W	Severity of non-bloody diarrhoea	-	V	Beta(1.5,21)	0.067	0.008	0.054	0.168
$\nu_{S,LS}$	Incidence rate lab confirmed STEC O157 gastro-enteritis	$year^{-1}$	U	Gamma(120,1/3)	40.0	34.2	39.9	46.2
$\pi_{M,S,LS}$	Case-fatality ratio lab confirmed STEC O157 gastro-enteritis	-	U	Beta(2,118)	0.0067	0.003	0.0014	0.039
$e_{M,G}$	Expected life span of a fatal case of STEC O157 gastro-enteritis	year	U + V	Discrete[2]	10.4	0.5	4.4	47.2

[1] U: uncertain, V: variable
[2] Characteristic values of the variability distribution are presented with uncertain parameters at their expected value

[5] For computational purposes, the disease burden per case is not simulated individually but for all cases together. First, for one episode of diarrhoea, the disease burden is simulated as the product of samples from the variability distributions for severity and duration:
$yld_{ui} = t_{ui} \times w_{ui}$
with u = iteration counter and i = B (bloody diarrhoea) or W (non-bloody diarrhoea).
Then, 10,000 samples of yld_{ui} were obtained and fitted to new Gamma distributions:
yld_B = Gamma (1.232, 1.792) and yld_W = Gamma (1.065, 0.211).
The product of N samples from a Gamma (a , b) distribution follows a Gamma (Na , b) distribution. Therefore, the variability in the disease burden at population level can be modelled as:
YLD_B = Gamma (N_B x 1.232, 1.792)/365 and YLD_W = Gamma (N_W x 1.065, 0.211)/365

4.2.2 HUS model

A stepwise summary of the HUS model is given on page 35, the parameter values are described in Table 4.2. In each iteration, a Poisson distribution represents the variability in the annual incidence of HUS for patients younger than 15 years (all causes). The uncertainty in the attributable proportion of STEC O157 is introduced at two levels. First, the uncertainty related to the actual proportion of all STEC –positive results that are due to serotype O157 is represented by a uniform distribution between the two extreme positions: only conclusive evidence for O157 is considered ($\psi_{S|H1} = 0.62$) or all STEC are O157 ($\psi_{S|H2} = 0.77$). Secondly, the uncertainty in the extreme values of $\psi_{S|H}$ is obtained by bootstrapping from the original case-control data. The model then simulates the total number of cases (all ages) by sampling from a Negative binomial distribution. Because of the low number of cases, the disease burden model is set up as a micro-simulation, in which the life history is simulated for each individual patient. First, the model simulates an individual expected life span at the age of developing HUS, see Appendix 6. At each step of the model, the age of the patient is compared with this life span, and the simulation is halted when the predicted age at death by other causes is reached. The age-distribution of HUS patients is sampled from a discrete distribution, based on observed data. The model then simulates if the patient survives the clinical phase of HUS by a Bernoulli trial. All transition probabilities (e.g. mortality ratios) are represented by Beta distributions, obtained by multiplying a Beta (0,0) prior with the likelihood function of the observed data. The Beta (0,0) prior is chosen because it does not affect the mean of the posterior distribution as compared to the maximum likelihood estimate. If the patient dies from HUS, the number of life years lost is calculated by subtracting the age at onset of HUS from the expected age at death. If the patient survives, the morbidity burden is sampled from a distribution of severity weights for one year with an episode of clinical HUS.

If the patient survives HUS, the model simulates whether the patient will develop direct ESRD. If this is not the case, the model simulates if the patient will develop late ESRD and if so, at which point in time. Patients who develop late ESRD will experience a gradual decline of their renal function that will negatively affect their quality of life before the diagnosis is made. The model approximates the disease burden by assuming that the severity weight increases linearly from 0 to an individual simulated severity weight for dialysis. Then, the morbidity burden can be calculated as 50% of the product of the time to late ESRD and the severity weight for dialysis. For patients who develop (late or direct) ESRD, the time to transplantation is then simulated. While on dialysis, there is an increased risk of death in the first year, which is simulated by a Bernoulli trial. If the patient dies, the mortality burden is calculated by subtracting the age halfway during the time to transplantation from the life span. If the patient survives, the morbidity burden is calculated as the product of the time to transplantation and the severity weight. Then, a Bernoulli trial is performed to simulate whether the patient survives the transplantation. If not, the mortality burden is calculated as the difference between the age at transplantation and the expected age at death. If the patient survives, the morbidity burden is sampled from the distribution of severity weights for a year including transplantation. The survival time of the functioning graft is then simulated, the age at graft rejection and the morbidity burden are calculated. If graft rejection occurs before the simulated individual life span, the patient enters another cycle of dialysis – transplantation – graft rejection. In the absence of data, parameter values for this cycle are the same as for the first cycle (but all simulations are based on new samples from these distributions). If the age at second graft rejection is less than the expected age at death, patients are assumed to depend on dialysis for the rest of their life.

a. Incidence of HUS in the Netherlands per year (one iteration)

i.	Simulate the incidence of HUS under 15	$N_{H<15} \sim \text{Poisson}(\nu_{H<15})$
ii.	Simulate attributable proportion STEC O157	$\psi_{S\|H<15}$
iii.	Calculate incidence STEC O157 ass. HUS < 15	$\psi_{H<15,S} \sim \text{Binomial}(\psi_{H<15}, \psi_{S\|H<15})$
iv.	Simulate proportion of cases under 15	$\pi_{H<15}$
v.	Calculate incidence STEC O157 ass. HUS all ages	$N_{H,S} \sim \text{NegBin}(\psi_{H<15,S}, \pi_{H<15})$

b. For each individual STEC O157 associated HUS patient in one iteration

vi.	Simulate age at onset of HUS	a_H
vii.	Simulate individual expected life span at HUS	e_H
viii.	Calculate expected age at death	$a_M = a_H + e_H$
	N.B. For any individual, the simulation is terminated if $a_i \geq a_M$	
ix.	Survive HUS?	$\text{Binomial}(1,\pi_{M\|H})$
x.	No:	$lyl_H = e_H$; stop
xi.	Yes: Simulate duration of clinical HUS	t_H
xii.	Simulate severity of clinical HUS	w_H
xiii.		$yld_H = t_H \times w_H$
xiv.	Develop direct ESRD?	$\text{Binomial}(1,\pi_{E\|H})$
xv.	Yes: go to step xxi	
xvi.	Develop late ESRD?	$\text{Binomial}(1,\pi_{lE\|H})$
xvii.	No: stop	
xviii.	Yes: Simulate time to late ESRD	t_{lE}
xix.	Calculate age at onset of (late) ESRD	$a_{lE} = a_H + t_{lE}$
xx.		$yld_E = t_{lE} \times w_D / 2$

c. For each individual ESRD patient in one iteration

xxi.	Simulate time to first transplantation	$t_{TX1} \sim t_{TX}$
xxii.	Calculate case-fatality ratio dialysis	if $t_{TX1} < 1$, $\pi_{M\|D1} = \pi_{M\|D*}$, else, $\pi_{M\|D1} = \pi_{M\|D*} / t_{TX1}$
xxiii.	Survive to first transplantation?	$\text{Binomial}(1,\pi_{M\|D})$
xxiv.	No:	$lyl_E = a_M - e_{ESRD}1/2$; stop
xxv.	Yes: Simulate severity of dialysis	$w_{D1} \sim w_D$
xxvi.		$yld_{D1} = t_{TX1} \times w_{D1}$
xxvii.	Calculate age at first transplantation	$a_{TX1} = a_{(l)E} + t_{TX1}$
xxviii.	Survive first transplantation?	$\text{Binomial}(1,\pi_{M\|TX})$
xxix.	No:	$lyl_{TX1} = a_M - a_{TX1}$; stop
xxx.	Yes: Simulate severity	$yld_{TX1} \sim w_{TX}$
xxxi.	Simulate graft survival	$t_{FG1} \sim t_{FG}$
xxxii.	Simulate severity functioning graft	$w_{FG1} \sim w_{FG}$
xxxiii.		$yld_{FG1} = t_{FG1} \times w_{FG1}$
xxxiv.	Calculate age at graft rejection	$a_{GR1} = a_{TX1} + t_{FG1}$
xxxv.	Repeat steps xxi-xxxiii for second graft	
xxxvi.	Calculate age at second graft rejection	$a_{GR2} = a_{TX2} + t_{FG2}$
xxxvii.	Calculate remaining life span	$t_{D3} = a_M - a_{GR2}$
xxxviii.	Calculate case-fatality ratio dialysis	if $t_{D3} < 1$, $\pi_{M\|D3} = \pi_{M\|D*}$, else, $\pi_{M\|D3} = \pi_{M\|D*} / t_{D3}$
xxxix.	Premature death by dialysis?	$\text{Binomial}(1, \pi_{M\|D3})$
xl.	Yes: Simulate age at death	$a_{M\|D3} = a_{GR2} + \text{Uniform}(0, t_{D3})$
xli.		$lyl = a_M - a_{M\|D3}$
xlii.	Simulate severity dialysis	$w_{D3} \sim w_D$
xliii.		$yld_{D3} = (a_{M\|D3} - a_{GR2}) \times w_{D3}$; stop
xliv.	No:	$yld_{D3} = t_{D3} \times w_{D3}$

xlv. d. For all HUS patients in one iteration

xlvi.	Calculate disease burden for one iteration:	$daly = \Sigma_i\, yld_i + \Sigma_i\, lyl_{,i}$
xlvii.	Repeat a - d for 1500 iterations = 1 simulation	
xlviii.	Repeat simulation 250 times with random samples from uncertain parameters	

Table 4.2. Parameters of the HUS model

Par.	Description	Unit	Type[1]	Distribution	Mean	5-perc.	Median	95-perc.
$\psi_{H<15}$	Incidence rate HUS under 15	$year^{-1}$	C	Constant	22	-	-	-
$\psi_{S\|H}$	Attr. prop. STEC O157 under 15	-	U	Uniform ($\psi_{S\|H1}$,$\psi_{S\|H2}$)	0.69	0.62	0.69	0.76
$\psi_{S\|H1}$	…only conclusive evidence	-	U	Bootstrapping, see 3.3.2	0.62	0.53	0.62	0.69
$\psi_{S\|H2}$	…all VTEC is O157	-	U	Bootstrapping, see 3.3.2	0.77	0.70	0.77	0.84
$\pi_{H<15}$	Proportion of HUS under 15	-	U	Beta (5, 13)	0.72	0.54	0.73	0.88
a_H	Age at onset HUS	-						
	under 15		V + U	Discrete, see 3.3.2	3.4	0.5	2.5	9.5
	…above 15		V + U	Uniform (15,100)	57.5	19.3	57.5	97.8
a_M	Expected life span at HUS	-	V + U	Discrete	dep. see	on age App.	at onset 6	HUS,
$\pi_{M\|H}$	CFR of HUS	-	U					
	under 65			Beta (32, 835)	0.037	0.027	0.037	0.048
	…above 65			Beta (10, 8)	0.56	0.36	0.56	0.74
t_H	Duration of clinical HUS	days	V	Uniform (14, 28)	21	15	21	27
w_H	Severity of clinical HUS	-	V	Discrete, see 4.1.2 and Table A5.2	0.93	0.73	1.00	1.00
$\pi_{E\|H}$	Prob. direct ESRD	-	U	Beta (23, 711)	0.031	0.022	0.031	0.043
$\pi_{lE\|H}$	Prob. late ESRD	-	U	Beta (8, 68)	0.11	0.05	0.10	0.17
t_{lE}	Time to late ESRD	year	V	Uniform (0, 40)	20	2	20	38
w_D	Severity weight dialysis	-	V	Discrete, see Table A5.3 and Fig. A5.1	0.18	0.00	0.13	0.57
t_{TX}	Time to transplantation	year	V + U	Weibull, see Appendix 3	dep.	on age	at onset	ESRD
$\pi_{M\|D*}$	CFR 1st year dialysis	-	U					
	…0-15			Beta (2, 40)	0.048	0.009	0.041	0.111
	…16-44			Beat (18, 185)	0.089	0.058	0.087	0.124
	…45-64			Beta (61, 102)	0.37	0.31	0.37	0.44
	…65-74			Beta (81,44)	0.65	0.58	0.65	0.72
	…75+			Beta (48,13)	0.79	0.70	0.79	0.87
$\pi_{M\|TX}$	CFR transplantation	-	U	Beta (3,36)	0.077	0.022	0.070	0.16
w_{TX}	Severity weight transplantation	-	V	Beta (18,82)	0.18	0.12	0.18	0.25
w_{FG}	Severity weight functioning graft	-	V	Beta (12, 88)	0.12	0.07	0.12	0.18
t_{FG}	Graft survival	year	V + U	Weibull, see Appendix 3	19.8	0.02[2]	4.0	90.3

[1] U: uncertain; V: variable; C: constant

[2] Characteristic values of the variability distribution are presented with uncertain parameters at their expected value: Weibull (0.47,8.75)

4.3 Results of the baseline model

Table 4.3 summarises the results of the baseline model, details can be found in Appendix 8. Incidence data for gastrointestinal illness and related mortality have already been discussed in detail in paragraphs 3.2.1 and 3.2.3. The mean incidence of D+ HUS (all ages) due to infection with STEC O157 is 22 cases per year, of which 15 children under 15 and 7 at higher ages. Of these, slightly more than 2 HUS cases have a fatal outcome, of which 1.5 aged 65 years and above. The renal damage due to HUS results in an annual mean of 2.5 cases of ESRD, of which 0.6 immediately after the HUS episode, and 2.0 at a later age. Of these 2.5 ESRD patients, 0.5 eventually die as a result of the effects of either dialysis or kidney transplantation.
The mean disease burden of STEC O157 associated illness is 116 DALY per year. Death in the clinical phase of HUS is the largest single contributing factor, with 58 DALY (50%), followed by death due to ESRD (21 DALY = 18%). Overall, fatal outcomes account for 87 DALY or 75% of the total disease burden. Morbidity accounts for 25% of the total disease burden, with dialysis due to ESRD and bloody diarrhoea as the most important factors.

Table 4.3. Burden of STEC O157 associated illness in the Netherlands (mean values per year)

	Number of cases	YLD	Number of fatalities	YLL	DALY
Total		***29.4***		***86.6***	***116.0***
Gastroenteritis	**2114**	**6.7**	**0.56**	**7.4**	**14.1**
Non-bloody diarrhoea	1118	0.7			0.7
Bloody diarrhoea	996	6.0	0.56	7.4	13.4
Haemolytic uraemic syndrome		**22.7**		**79.2**	**102.0**
Clinical phase	21.7	1.0	2.2	57.8	58.8
First dialysis period	2.5	4.0	0.2	4.0	8.0
First transplantation	2.1	0.3	0.2	8.9	9.2
Life with functioning graft	2.0	3.0	-		3.0
Second dialysis period	1.7	3.3	0.1	3.0	6.3
Second transplantation	1.5	0.3	0.1	5.4	5.7
Life with functioning graft	1.4	2.0	-		2.0
Third dialysis period	1.0	8.8	0.03	0.1	8.9

Note that due to the stochastic nature of the model, not all summations do necessarily tally.

4.4 Uncertainty and variability

The second-order Monte Carlo model used to calculate the disease burden allows separate evaluation of uncertainty and variability in the average estimates given in paragraph 4.3. The model is set up as a series of 250 simulations, with 1500 iterations each. Each simulation calculates the variability of the disease burden, for a particular set of uncertain input parameters. Hence, the difference between results of different simulations quantifies the uncertainty in the model results. Graphically, this can be represented as in Figure 12. In this figure, the results of 250 simulations have been sorted according to the mean result for total DALYs, that ranges between 68 and 223. The 90% confidence interval for the mean burden

is 84-159, see Table 4.4. The figure also shows the median of each simulation, which is very similar to the mean, indicating that the output distributions are relatively symmetrical. The 5- and 95-percentiles of each simulation indicate the variability of the disease burden. It can be seen that the variability increases slightly with increasing mean and that variability is larger than uncertainty. The relative importance of uncertainty and variability can be quantified by the variance ratio: $F = \sigma^2_{var} / \sigma^2_{unc} = (76.6/23.3)^2 = 10.8$. In other words, the effect of variability is approximately 11 times bigger than the effect of uncertainty.

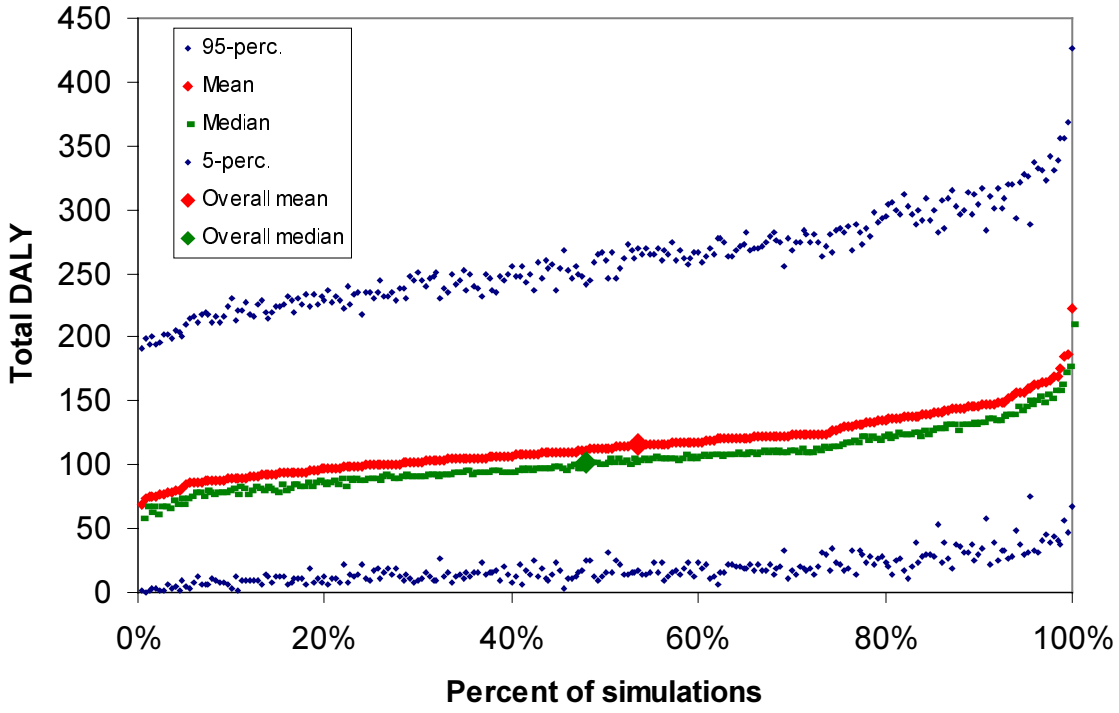

Figure 12. Uncertainty and variability in total DALY estimate

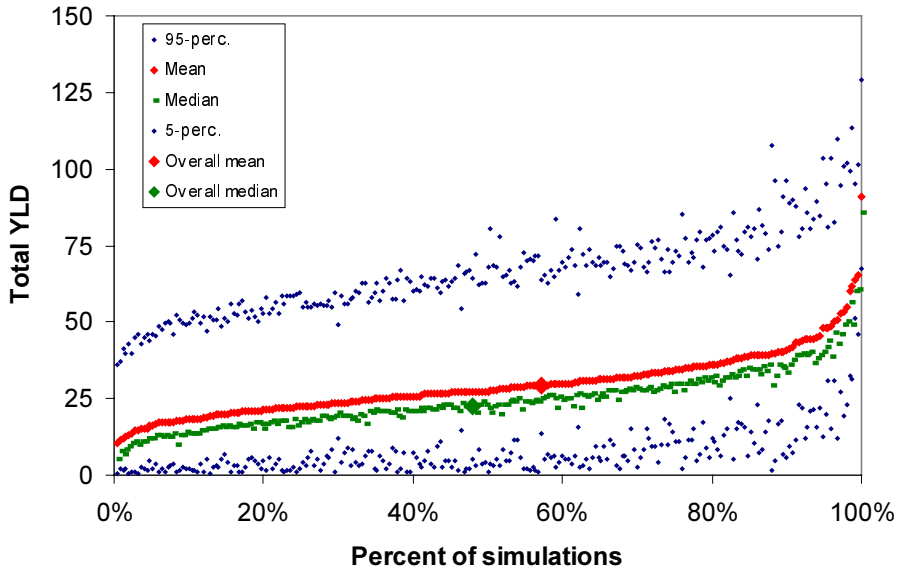

Figure 13. Uncertainty and variability in total YLD estimate

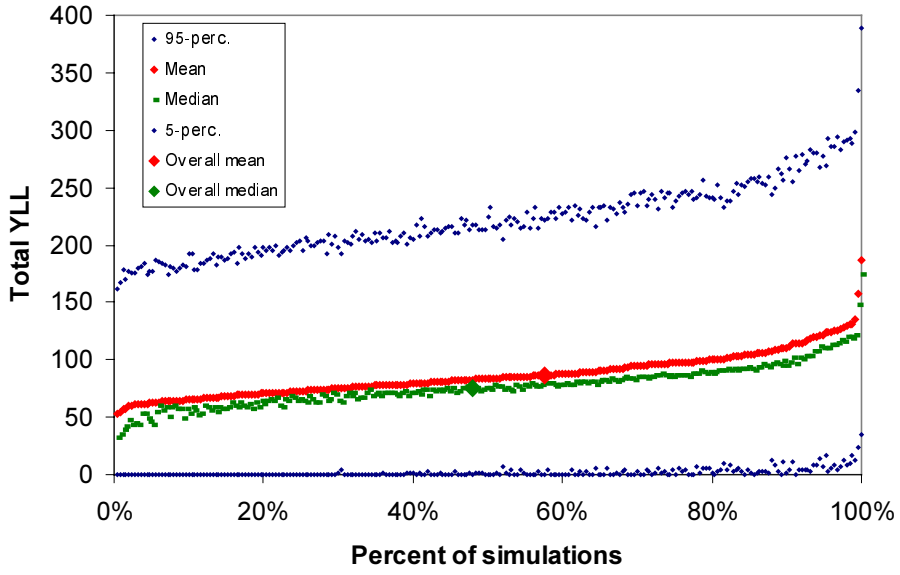

Figure 14. Uncertainty and variability in total YLL estimate

Figure 13and Figure 14 show the relative effects of variability and uncertainty for YLD and YLL, some statistics are shown in Table 4.4. The relative contribution of variability is largest in YLL, which is related to the low numbers of fatal cases and a wide age range for these cases.

Table 4.4. Summary statistics of output distributions

	Mean of means	5-p. of means	Median of means	95-p. of means	SD of means (unc.)	Mean of SDs (var.)	F-ratio	Median of medians
DALY	116.0	84.9	116.0	158.5	23.3	76.6	10.8	101.8
YLD	29.4	16.7	29.4	47.9	10.3	21.8	4.5	22.7
YLL	86.6	62.5	86.6	122.6	19.0	72.1	14.4	75.2

4.5 Sensitivity analysis

In constructing the baseline model, many choices were made: to use one data-source or another or a combination of data-sources, how to use a particular correction factor etc. These choices involved judgements about the nature of the data in relation to the representativeness of the model, but alternative choices would also have been defensible. In this paragraph we examine the effect of several alternative choices on the outcomes of the model.

Scenario 1. In paragraph 3.2.1, the correction for underreporting of NIVEL surveillance data (consultations of general practitioners for gastroenteritis) is described. The baseline scenario is based on an incidence of 13.8 consultations per 1,000 pyr. The uncorrected figure is 8.0 consultations per 1,000 pyr, whereas the maximum estimate was 35 consultations per 1,000 pyr. In the baseline scenario, 2.18 x 10^5 consulations per year are expected in the Netherlands, in the alternative scenarios these figures would be 1.26 resp. 5.53 x 10^5 per year. Based on these figures, alternative estimates for the incidence of STEC O157 associated bloody / non-bloody diarrhoea are 360 / 410 (scenario 1a) and 1570 / 1760 (scenario 1b) cases per year.

Scenario 2. Duration of diarrhoea was based on relatively few data and duration in children (the age group with the highest incidence) could be higher. In the alternative scenario, we use data as observed in an outbreak in a day-care centre: 12 days for bloody and 7 days for non-bloody diarrhoea (see paragraph 3.2.2).

Scenario 3. The case-fatality ratio for gastro-enteritis is highly uncertain. In this scenario, we use four different values (0.1, 0.3, 1 and 3%) around the baseline estimate of 1.4%.

Scenario 4. In the baseline model it is assumed that the life expectancy of fatal cases of gastroenteritis is the same as for the general population. It is possible that those who die from gastroenteritis have underlying diseases and consequently a lower life expectancy. Therefore, the life expectancy of fatal cases was varied in this scenario between 0.3 and 10 years. Alternatively, the outcomes of this scenario could be considered to account for a lower quality of life of fatal cases, had they not died (i.e. the severity weight for death is less than 1).

Scenario 5. In this scenario, we evaluate the effect of uncertainty in the proportion of HUS cases that is attributable to infection with STEC O157, by assuming that only culture-positive evidence is a valid indication of an etiological role of STEC O157 ($\psi_{S|H} = 0.62$) or all cases with ST in the faeces are attributable to STEC O157 ($\psi_{S|H} = 0.77$), see paragraph 3.3.2).

Scenario 6. In this scenario, we do not use the long-term follow up data on the probability of developing late ESRD, as reported in France, but only use follow-up data, as reported in the Netherlands and Belgium. These data represent a shorter period of approximately 10 years and a considerably lower probability of developing ESRD (2.7 vs. 10%), see paragraph 3.3.5).

Table 4.5. Alternative parameter values in scenario analysis

Scenario	Parameter	Default value	Alternative value
1a	ν_B / ν_W	590 / 667	360 / 410
1b			1570 / 1760
2	t_B / t_W	5 / 3	12 / 7
3a	$\pi_{M,LS,S}$	1.4%	0.1%
3b			0.3%
3c			1%
3d			3%
4a	$e_{M,G}$	4.4	0.3
4b			1
4c			3
4d			10
5a	$\psi_{S\|H}$	0.69	0.62
5b			0.77
6	$\pi_{I\|E\|H}$ / $t_{I\|E}$	0.10 / Uniform (1,40)	0.027 / Uniform (1,10)

Univariate scenario analyses were performed by setting all uncertain parameters in the model at their median value, and replacing the alternative values in different scenarios as indicated in Table 4.5. The model was then run for 1500 iterations to simulate the disease burden. The results for mean simulated burden are shown in Figure 15. Note that the mean in the baseline scenario (108 DALY per year) is lower than reported in Table 4.3. This is due to the fact that these simulations did not include possible high values for uncertain parameters.

Most scenarios relate to parameters that influence YLD or YLL by gastroenteritis, and these factors have a relatively small effect on the overall disease burden. The figure shows that

YLD GE is relatively high in scenarios 1b and 2, but the total disease burden only increases by 5 DALY per year.
The most important effects on the model output are observed in scenarios 5 and 6. Increasing the fraction of HUS cases that is attributable to STEC O157 infection to 0.77 increases YLL HUS from 82 to 91 and YLD HUS from 20 to 23, resulting in an increase of the total disease burden from 108 to 120 DALY. It must be noted that it is well established in the literature that other STEC serotypes are also able to induce HUS, so this output may overestimate the true disease burden. On the other hand, the method to detect Shiga-like toxin is limited in sensitivity and accounting for this factor may increase the estimate of the true attributable fraction. In scenario 6, YLL due to HUS (including ESRD) decreases to 69 and YLD to 9. This reduces the total disease burden to 85 DALY (a decrease of 21%). Comparing these results with the 5-percentile of the uncertainty of mean burden in the complete model (84.9 - 158.5, Table 4.4) indicated that the probability to develop ESRD is one of the most important sources of uncertainty in the model.

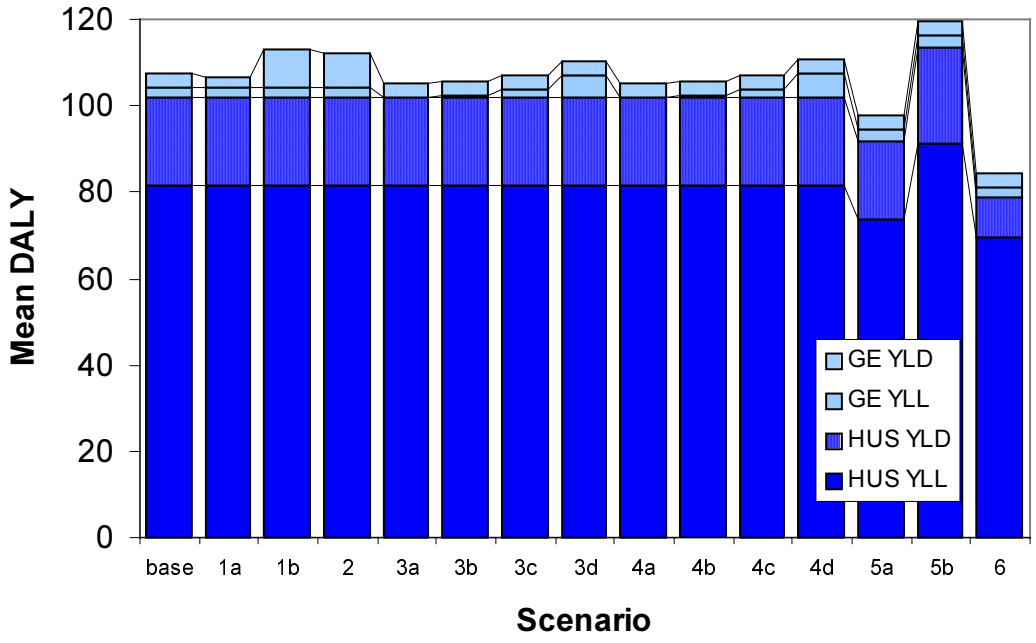

Figure 15. Results of scenario analysis

The most important contribution to the total disease burden is made by HUS-related mortality. We therefore separately evaluated the effect of uncertainty in the case-fatality ratio of HUS on the model results. The parameter $\pi_{M|H}$ for age categories under and over 65 years was set at the 1, 5, 50, 95 and 99 percentile values of the distributions defined in Table 4.2, see Table 4.6.

Table 4.6. Alternative values for case-fatality ratio of HUS in two different age groups

Scenario	$\pi_{M\|H}$
Under 65	
1-perc.	0.024
5-perc.	0.027
50-perc.	0.037
95-perc.	0.048
99-perc.	0.053
Over 65	
1-perc.	0.291
5-perc.	0.364
50-perc.	0.556
95-perc.	0.740
99-perc.	0.800

The range of parameter values reflects the larger uncertainty in the case-fatality ratio over 65 years, due to a lower number of observations. However, the results, as shown in Figure 16, demonstrate that the total disease burden is most sensitive to the (relatively small) uncertainty in the case-fatality ratio under 65 years. This can be explained by the high number of life years lost by one fatal case among children. In these scenarios, the total disease burden ranges between 90 and 125 years, less than the range of uncertainty in the complete baseline model (Table 4.4).

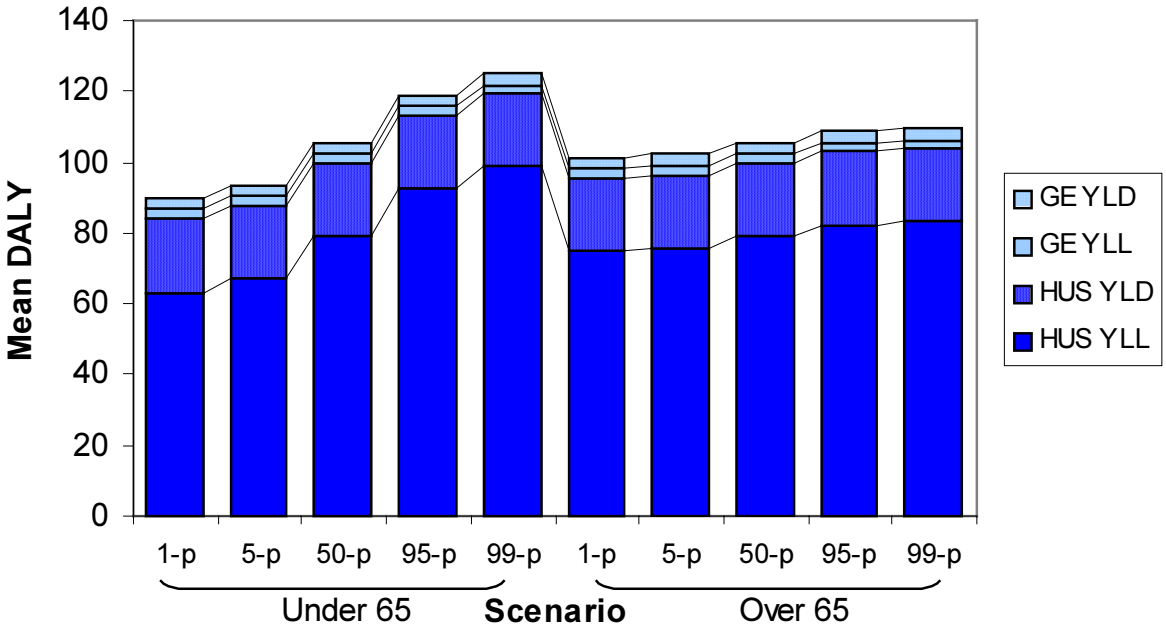

Figure 16. Sensitivity of model output to uncertainty in the case-fatality ratio of HUS in two age groups

5. Discussion

The diarrhoeal illness associated with infection by Shiga toxin producing *E. coli* O157 is relatively severe, and a high proportion of infected children suffers from haemolytic uraemic syndrome. To quantify the burden of disease by STEC O157 in the Netherlands, and to compare this burden with that caused by other illnesses including by other enteropathogens, we used the concept of Disability Adjusted Life Years (DALYs). The incidence of STEC O157 related disease in the Netherlands is low with a median of 1250 and a mean of 2100 cases of gastroenteritis and 22 cases of HUS per year. Nevertheless, we estimate that approximately 120 DALYs per year are lost by these illnesses. A previous study [40] estimated the disease burden of campylobacteriosis in the Netherlands in the early nineteen-nineties as 1400 DALYs per year. On an absolute basis, campylobacteriosis is more significant from a public health perspective. It was also estimated that the incidence of Campylobacter associated gastroenteritis was 318,000 cases per year. Thus, the burden of campylobacteriosis is 4.4 DALYs per 1000 cases, whereas it is 55 DALYs per 1000 cases of STEC O157 associated gastro-enteritis. Thus, on a case per case basis, STEC O157 has a more than 12-fold higher health impact than *Campylobacter*. Any outbreak or increase in incidence of STEC O157 will be significant for public health.

As in the previous study, the DALY concept proved a flexible and robust tool to estimate the impact of infectious intestinal illness on public health. The robustness of the final estimates is based in part on the aggregate nature of the estimates. Different disease end-points contribute to the overall disease burden, and it is not likely that all estimates simultaneously are biased in the same direction. This does not put aside the fact that there is considerable uncertainty in the underlying estimates and hence in the estimated disease burden. The major sources of uncertainty are the (lack of) epidemiological data, and in particular the incidence of gastroenteritis due to STEC O157, and the fraction of HUS that is attributable to STEC O157.

The second order Monte Carlo approach used in this report allows separate evaluation of the effects of variability and uncertainty in the model parameters. Overall, uncertainty was only found to be of major importance for the incidence estimate of STEC O157 associated gastroenteritis, and consequently also YLD due to GE. For all other factors in the model, and for the aggregated estimates of YLD, YLL and DALY, variability was much greater than uncertainty, even though several parameter estimates were highly uncertain. This is mainly related to the fact that there is only a low number of cases of HUS and related death or ESRD per year. Hence, even if incidence rates are constant in time (as was assumed in this model), the actual number of cases per year will show important variation. Our results also show that scenario uncertainty (e.g. to base parameter estimates on one particular study, or to use the results of another study) does not have a major impact on the estimate of the total disease burden.

The uncertainty in the incidence estimate for STEC O157 associated gastroenteritis is mainly caused by the low number of positive stools in the SENSOR and NIVEL studies (respectively 0 and 1) and the absence of direct information on the GP consultation pattern of STEC O157 cases with gastroenteritis. As a consequence, the uncertainty distribution of the incidence is extremely skewed with a mode of 0, a median of 1200 and a mean of 2000 cases per year. The probability that the mean underestimates the true incidence is only 33% and it is therefore more likely that the true incidence is lower than the simulation mean.

Table 5.1. International comparison of incidence rates of STEC O157 associated gastroenteritis by different surveillance systems (sources: see text)

Country	**Incidence rate per 100,000 pyr**		
	Population[1]	General practice	Laboratory surveillance
the Netherlands	13	1.7	0.25
England and Wales	-	3	2.5
United States	27	-	1.3
Ontario, Canada	21	-	3

[1] All population estimates are extrapolated from either general practice (NL) or laboratory surveillance (USA, CAN) data. An extrapolation factor for England and Wales has not been reported

Table 5.1 compares the incidence estimates for STEC O157 associated gastroenteritis in the Netherlands with literature data for England and Wales, and for the United States. Wheeler *et al*. [92] employed a study design similar to the SENSOR study and did not detect any infections with STEC O157 among 781 cases of gastroenteritis in the general population, which is similar to the Dutch results (no STEC O157 among 699 cases of gastroenteritis). In the same UK study, the incidence rate of STEC O157 patients reporting to their general practitioner was estimated at 3 per 100,000 personyears, which is about twice as high as the Dutch estimate. In the UK study, an average of 5.8 community cases were observed for each GP case, whereas in the Netherlands this number is much higher (20:1, using the GP consultation rate from the SENSOR study). For bacterial pathogens, the ratio of community to GP cases in the UK was as low as 2.1:1 (*Campylobacter*) or 1.4:1 (*Salmonella*). This report estimates a ratio of community to GP cases of 7.6:1 (90% CI 3.7 - 14.3) for STEC O157 in the Netherlands. It therefore seems likely that the difference in observed incidence of STEC O157 in general practices is at least partly associated with different GP consultation patterns in the two countries. The reported incidence of STEC O157 in laboratory surveillance in the Netherlands is very low compared to the UK data [61]. This might also be related to differences in physician's choices to request faecal cultures, or in laboratory practices to routinely include culture for STEC O157, as well as to true differences in incidence. Indeed, in England and Wales, it is recommended that every stool specimen be cultured for STEC O157 and this has been common practice in Wales since the early nineteen-nineties. In the Netherlands, only 8% of medical laboratories routinely test for STEC O157 in all faecal samples. Other laboratories test only a selection of samples, based on clinical observations such as bloody diarrhoea or HUS [85].

In the United States, no recent surveillance data at population or general practice level are available. Mead *et al*. [50] reported estimates of the incidence of intestinal pathogens, based on a variety of sources including active and passive (laboratory) surveillance and presented crude estimates for underreporting. The FoodNet active surveillance system produced a weighted incidence rate of 1.34 cases per 100,000 population, which was multiplied by an arbitrary factor of 20, resulting in an estimated incidence rate of 27 per 100,000 pyr in the general population. Again, both estimates are higher than those in the Netherlands are.

In Canada, large geographical differences exist in reported incidence rates of STEC O157 associated gastroenteritis. Between 1987 and 1991, the reported incidence in the Province of Alberta was as high as 12.1 per 100,000 pyr [91]. More recently, Michel *et al*. [51] reported an average incidence rate of approximately 3 per 100,000 pyr for the Province of Ontario. Another paper by the same authors [52] estimated that for each reported case, between 4 and 8 community cases were not reported to the surveillance system. Combining these data results in an estimated incidence rate of 21 symptomatic cases per 100,000 pyr.

Thus, the estimated incidence rate of STEC O157 associated gastroenteritis in the Netherlands is lower than in several (Anglo-Saxon) countries. This may partly be explained by differences in reporting systems, but probably reflects a true difference in incidence in the population. The low number of recognised outbreaks in the Netherlands supports the latter hypothesis. Finally, it is suggested that laboratory surveillance in the Netherlands identifies a smaller proportion of all cases than in other countries. This is partly due to a lower proportion of patients who actually visit their GP.

Table 5.2. International comparison of incidence rates of HUS (all causes)

Coutry	**Period**	**Age group**	**Incidence HUS per 100,000**	**Reference**
the Netherlands	1990-2000	< 5	2.0	This study
		< 15	0.7	
		all ages	0.18	
France	1993-1996	< 5	1.8	[25]
		< 15	0.7	
Australia	1994-1998	< 15	0.64	[29]
Belgium	1996	< 5	4.3	[60]
		< 15	1.8	[60]
Germany	1997-2002	< 15	0.7	[35]
Austria	1997-2002	< 15	0.4	[35]

Table 5.2 compares the data from this study with some international data in incidence rates of HUS. As in all countries, the incidence rate of HUS in the Netherlands is highest in the age group under 5 and similar to data for France in that group. In the age group under 15 (including under fives), the incidence rate in the Netherlands is similar to France, Australia and Germany. Belgium reports a higher incidence rate, whereas Austria reports lower values.

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Appendix 1 Statistical analysis of data on gastroenteritis

A. Uncertainty in the incidence of STEC O157 associated gastrointestinal illness in the Netherlands, based on the SENSOR study

a. Classical statistics[6]

Let N_S be the observed number of cases of *STEC* O157 associated gastroenteritis in a survey with T personyears in a population with an incidence rate υ_S. Assume that N_S follows a Poisson ($\upsilon_S.T$) distribution. Then, the probability of finding 0 cases is $p(N_S=0)=e^{-\upsilon_S.T}$. A (1-α) confidence interval for υ_S may be found as $\{\upsilon_{S,0}$: H_0: $\upsilon_S=\upsilon_{S,0}$ vs. H_1: $\upsilon_S<\upsilon_{S,0}$ is accepted at level α using $N_S=0$ as critical region$\}$. A particular $\upsilon_{S,0}$ will be accepted at level α if $P(N_S=0|\upsilon_S=\upsilon_{S,0})>\alpha$. Since $P(N_S = 0)=e^{-\upsilon_S.T}$, the confidence interval exists of those $\upsilon_{S,0}$ for which $\alpha>e^{-\upsilon_{S,0}.T}$. The upper limit on υ_S is obtained from $\alpha=e^{-\upsilon_{S,0}.T}$, i.e. $\upsilon_{S,0}=-\ln(\alpha)/T$. In the SENSOR study, T= (699/1050) x 2229 = 1484 pyr for cases with stool examination for STEC. Hence at a 95% level, the upper limit on the incidence rate υ_S is $\upsilon_{S,0}=-\ln(0.05)/1484=0.00202$ pyr^{-1}. For a population of 15.6 million, the upper limit for the crude incidence is 31,500 cases per year. Assuming that standardisation would affect this estimate by the same factor as the total incidence of gastroenteritis (i.e. the age distribution of total and *STEC* O157 associated gastroenteritis is similar), the upper bound for the standardised incidence would be 19,000 cases per year.

b. Bayesian statistics

Let N_G be the observed number of cases of all gastro-enteritis in a survey with T personyears in a population with an incidence rate υ_G. Assume that N_G follows a Poisson ($\upsilon_G.T$) distribution. Using a Gamma (1/z, z) prior with z approaching infinity, the posterior distribution for υ_G is Gamma(N_G,1/T). Let π_S be the proportion of all cases by STEC O157. In this case, there is strong reason to suggest that the true value of π_S will be low, say less than 1%. A Beta (0.02, 4) distribution has a mean of 0.5% and a 95% upper limit of 1.3%, and therefore appears a suitable prior distribution. Given the observed data, the posterior distribution for π_S is Beta (0.02, 703). The incidence of STEC O157 associated gastroenteritis in the Netherlands is then estimated as $N_S= \upsilon_G$ x π_S x15600000. The uncertainty in N_S is estimated by Latin Hypercube sampling using @RISK4.0 (Pallisade Corporation, Newfield, NY, USA). The output distribution has a mean of 211 cases per year, 95%-ile 484 and maximum 41 000 cases per year. The probability of zero incidence is approximately 90%. Applying the same correction factor for standardisation as above, the median incidence is 0, mean 121 cases per year, 95%-ile 291 and maximum 18 000 cases per year. The output distribution is very sensitive to the choice of the prior distribution, hence the estimates have a high degree of subjectivity.

B. Uncertainty in the incidence of GP consultations, based on the SENSOR study and the fraction attributable to STEC O157

The table shows the standardisation of incidence rates for all cases of gastroenteritis and GP consultations, based on raw data from the SENSOR study. In contrast to [19], we only standardise for age and not for cohort and sex. This is mainly because otherwise, there would be subgroups with no GP consultations in the middle age classes. Comparison of the

[6] Suggested by Dries de Wet, Johannesburg, South Africa

standardised incidence rate in the SENSOR study (0.283 per pyr) with the standardised incidence rate in this study (0.295 per pyr) shows that the difference is small. The uncertainty in the standardised incidence rates was obtained by Bayesian methods. The observed number of $N_{G,GP,i}$ cases in each age class is assumed to arise from a Poisson process with underlying incidence rate $\upsilon_{G,i}$ and observation time T_i for each age class. Then, $\upsilon_{G,i}$ ~ Gamma ($N_{G,GP,i}$, 1/ T_i) and $\pi_{G,i}$ ~ Poisson ($\upsilon_{G,i}$. N_i). The observed number of $N_{GP|G*,i}$ consultations among $N_{G*,i}$ respondents to questionnaires is assumed to result from a binomial process with underlying probability of consulting a general practioner $\pi_{GP|G*,i}$. Then, $\pi_{GP|G*,i}$ ~Beta ($N_{GP|G*,i}$, $N_{G*,i}$ - $N_{GP|G*,i}$). The incidence of GP consultations for gastroenteritis is estimated using the normal approximation of the binomial distribution:
$\upsilon_{G,GP,i}$ ~ Normal ($\upsilon_{G,i}.\pi_{GP|G*,i}$, $\sqrt{\{\upsilon_{G,i}.\pi_{GP|G*i,}\ (1-\pi_{GP|G*,i})\}}$).
The uncertainty in the standardised estimates is estimated by Latin hypercube sampling.

Table A.1. Simulation of the uncertainty in the incidence of gastroenteritis

Age group	N_i	T_i	$N_{G,i}$	$\upsilon_{G,i}$	$\pi_{G,i}$	$N_{G*,i}$	$N_{GP\|G*,i}$	$\pi_{GP\|G*,i}$	$\pi_{G,GP,i}$	$\upsilon_{G,GP,i}$
0	2.00E+05	311	237	0.762	1.52E+05	182	29	0.159	2.43E+04	
1-4	7.76E+05	419	372	0.888	6.89E+05	253	21	0.083	5.72E+04	
5-11	1.38E+06	444	224	0.505	6.96E+05	119	7	0.059	4.09E+04	
12-17	1.11E+06	307	49	0.160	1.77E+05	15	1	0.067	1.18E+04	
18-64	1.02E+07	420	104	0.248	2.52E+06	51	1	0.020	4.94E+04	
65+	2.13E+06	328	64	0.195	4.16E+05	24	2	0.083	3.46E+04	
Crude	1.58E+07	2229	1050	0.471	7.42E+06	644	61	0.095	7.03E+05	
Stand.				0.295	4.65E+06				2.18E+05	0.014

Legend (the subscript *i* refers to different age classes):
N_i Number of persons in the Dutch population, 1999 (CBS)
T_i Observation time (pyr)
$N_{G,i}$ Observed incidence of gastroenteritis
$\upsilon_{G,i}$ Inferred incidence rate of gastroenteritis in the general population (pyr^{-1})
$\upsilon_{G,i}$ Inferred incidence of gastroenteritis (yr^{-1})
$N_{G*,i}$ Number of cases with gastroenteritis who participated in the case-control study
$N_{GP|G*,i}$ Number of cases with gastroenteritis who participated in the case-control study who consulted a GP
$\pi_{GP|G*,i}$ Probability of consulting a GP for a case with gastro-enteritis
$\upsilon_{G,GP,i}$ Inferred incidence of GP consultations for gastroenteritis (yr^{-1})
$\upsilon_{G,GP,i}$ Inferred incidence rate of GP consultations for gastroenteritis (yr^{-1})

The uncertainty in the fraction of all GP consultations, attributable to STEC O157 is simulated as $\pi_{GP,S|G}$ ~ Beta (1, 797), i.e. a prior Beta (0,0) distribution multiplied by the binomial likelihood of observing 1/798 cases. Finally, the incidence of GP consultations due to gastroenteritis by STEC O157 is estimated as $\upsilon_{S,GP,,i}$ ~ Poisson ($\upsilon_{G,GP,i}$. $\upsilon_{GP,S|G}$).

C. Estimation of cases in the total population from GP consultations

Let N_S be the annual incidence of symptomatic cases (bloody and non-bloody diarrhoea) in the population, with $\pi_{B|S}$ the proportion of bloody diarrhoea and $\pi_{W|S}$ = (1-$\pi_{B|S}$) the proportion of non-bloody diarrhoea. Michel *et al*. [52], Table 1 show 253/538 unselected cases of STEC O157 associated diarrhoea are bloody. Then $\pi_{B|S}$ follows a Beta (254,286) distribution (using a uniform Beta(1,1) prior).
Let $\pi_{GP|B}$ be the proportion of patients with bloody diarrhoea who seek medical attention and $\pi_{GP|W}$ the proportion of patients with watery diarrhoea who do so. Estimates come from De Wit *et al*. [24] who reported that in the SENSOR study, 2 out of 9 patients with bloody diarrhoea and 59 out of 635 patients with watery diarrhoea consulted their GP. Using uniform

priors, $\pi_{GP|B}$ ~ Beta (3, 8) and $\pi_{GP|W}$ ~ Beta (60, 577). The overall proportion reporting to a GP is $\pi_{GP|S} = \pi_{B|S}.\pi_{GP|B} + \pi_{W|S}.\ \pi_{GP|W}$. Let $\pi_{S,GP}$ be the inferred incidence of GP consultations due to gastroenteritis by STEC O157. This can be considered the number of "successes" in a binomial process with a total of υ_S cases and a probability of success $\pi_{GP|S}$. The number of cases who did not consult a GP follows a negative binomial distribution and the incidence of all STEC O157 cases in the population can be estimated as
υ_S ~ NegBin ($\upsilon_{S,GP}$ +1, $\pi_{GP|S}$) + $\upsilon_{S,GP}$ [88]. Similar considerations lead to a distribution for the proportion of asymptomatic cases, based on the observed 50/279 cases: $\pi_{A|S}$ ~ Beta (51,230).

D. Reconstructing the case control study in SENSOR

The expected number of STEC O157 isolations in the SENSOR case control study can be reconstructed from the simulation results. Let $\check{N}_S$ be the simulated incidence of population cases of STEC O157 related illness and N the size of the Dutch population. Then the simulated incidence rate of STEC O157 related illness $\upsilon_S = \check{N}_S/N$. The expected number of cases in SENSOR is then calculated by multiplication with observed person time T and the fraction of gastro-enteritis cases that was actually sampled in the case control study N_{G*} / N_G. Assuming random effects, the actual number of observed cases follows a Poisson distribution.

E. Uncertainty in the age-distribution of STEC O157 associated gastrointestinal illness, based on laboratory surveillance

Let $N_{S,LS,i}$ be the reported number of laboratory confirmed cases of STEC O157 associated gastroenteritis in age group i, in a survey with $N_{S,LS} = \Sigma N_{S,LS,i}$ observations. Then, $N_{S,LS,i}$ follows a multinomial distribution. Using a Beta (0, 0)[7] prior, the uncertainty in the proportion of persons in the first age class can be represented by $\upsilon_{S,LS,1}$ ~Beta ($N_{S,LS,1}$, $N_{S,LS}$ - $N_{S,LS,1}$). For the second fraction, the same principle then yields $\upsilon_{S,LS,2}$ ~ [Beta ($N_{S,LS,2}$, $N_{S,LS}$ - $N_{S,LS,1}$ - $N_{S,LS,2}$)] (1- $\upsilon_{S,LS,1}$) etc. For the last fraction, $\upsilon_{S,LS,k} = 1 - \Sigma \upsilon_{S,LS,i}$.
The same method is applied to simulate the uncertainty in the age-distribution of fatal cases of gastroenteritis.

F. Uncertainty in the case-fatality ratio of STEC O157 associated gastro-enteritis

Let $N_{S,LS}$ be the number of cases of STEC O157 associated gastroenteritis in laboratory surveillance, and $N_{M,S,LS}$ be the number of fatal cases among them.
Then $\pi_{M,S,LS}$ = Beta ($N_{M,S,LS}$, $N_{S,LS}$ - $N_{M,S,LS}$). For 1999-2001; $N_{S,LS}$ = 120 and $N_{M,S,LS}$ = 2, hence $\pi_{M,S,LS}$ = Beta (2,118).

[7]Let π be the parameter of a binomial distribution. x positives are observed among a total of n tests. Using a Beta (a,b) prior, the posterior distribution for π follows a Beta ($x+a$,$n-x+b$) distribution. A uniform Beta(1,1) prior is recommended [88]. In the case of small numbers of (positive) observations, the choice of a and b significantly influences the posterior distribution and a uniform prior may shift the expected value away from the maximum likelihood estimate for π (= x/n) to $(x+a)/(n+b)$. The Beta (0,0) distribution, while mathematically undefined, is an acceptable alternative prior distribution that does not affect the expected value of the posterior distribution [34]. Note that the 90% credible interval of this posterior distribution is smaller than the MLE based interval.

Appendix 2 Probability of HUS as a consequence of STEC O157 associated gastroenteritis outbreaks

Location	Year(s)	Age range (median)	GE	HUS	%	Ref.
Minnesota, USA	1988	0-3	38*	5	13	[4]
Scotland	1992	0-3	4	1	25	[11]
Bangor, UK	1995	0-7	19	2	11	[1]
USA	1984	0-9(2)	36	3	8	[77]
Netherlands	1998	children	3	1	33	[42]
Connecticut, USA	1993	< 5	18	0	0	[64]
Scotland	1996	children(6)	40	6	15	[27]
UK (18 outbreaks)	1991-4	children	69	31	45	[89]
Washington State, USA	1993	children	371	39	11	[10]
Sakai, Japan	1996	6-12	8150	106	1	[81]
Minnesota, USA	1988	9-15	32	0	0	[5]
Massachusets, USA	1991	2-70(11)	23	4	17	[6]
USA	1996	1-46	70	14	20	[16]
Washington State, USA	1993	non-children	130	6	5	[3,10]
Utah, USA	1990	residents(25)	20	8	40	[59]
Birmingham, UK	1987	0-71(25)	26	1	4	[69]
Wisconsin, USA	1988	(28)	61	0	0	[65]
Sakai, Japan	1996	18-61(30)	47	3	6	[90]
Las Vegas, USA	1992-3	0-83(31)	58	3	5	[15]
Washington State, USA	1986	1-78(36)	37	4#	11	[58]
Cabool, Miss., USA	1990	(38)	243	2	1	[80]
Conn./Ill., USA	1996	2-87(43)	43	3	7	[43]
Connecticut, USA	1993	5-72	18	0	0	[64]
Sunderland, UK	1995	2-89(50)	12	2	17	[78]
Utah, USA	1990	employees	30*	0	0	[59]
UK (18 outbreaks)	1991-4	adults	104	5	5	[89]
Scotland	1996	adults(71)	222	22	10	[27]
Nebraska, USA	1984	(89)	34	1	3	[68]

* including asymptomatic infections
# reported as HUS and TTP

Appendix 3 Mortality and end stage renal disease as a consequence of HUS

Table A 3.1 summarises the literature on case series of D+ HUS patients and related fatalities in the acute phase of illness. There is one reference from the Netherlands, with 16/95 deaths in the period 1965-1977. However, most deaths occurred before 1973 and there were only 2/34 (5.9 %) fatal cases after 1973. Due to the low number of cases, there is considerable uncertainty in the estimate of the case-fatality ratio. Using additional data from other countries can reduce this uncertainty. The overall case-fatality ratio from international studies is 32/867 (3.7 %). These two estimates for the case-fatality ratio are not significantly different (Fisher's exact test), hence the pooled estimate will be used: $\pi_{M|H} \sim$ Beta (32, 835).

Table A3.1. Case-fatality ratio of HUS

Country	Period	Deaths	HUS patients	Reference	Comments
NL	1965-77	2	34	[21]	data after 1973
USA	1979-88	3	101	[48]	
UK	1966-85	2	68	[30]	data after 1980
Canada	1986-88	6	226	[66]	
USA	1971-90	6	140	[73]	
B	1970-82	4	83	[45]	
FRG	1971-88	3	59	[82]	
FR	1955-90	2	21	[63]	
USA	1991	2	21	[57]	
UK	1986-96	2	114	[75]	
Total		32	867		

Table A3.2 summarises the literature on direct ESRD in survivors of D+ HUS. There is one reference from Belgium and the Netherlands with 1/51 (2.0 %) direct ESRD cases. Due to the low number of cases, this estimate is highly uncertain. Using additional data from other countries can reduce this uncertainty. The pooled probability of ESRD from international studies is 23/734 (3.1 %). These two estimates for the ratio of direct ESRD to HUS are not significantly different (Fisher's exact test), hence the pooled estimate will be used: $\pi_{E|H} \sim$ Beta (21, 711).

Table A3.2. Probability of direct ESRD as a consequence of HUS

Country	Period	ESRD	HUS survivors	Reference	Comments
B/NL	1970-76	1	51	[87]	
USA	1979-88	11	98	[48]	
UK	1966-85	3	98	[30]	
Canada	1986-88	4	220	[66]	
USA	1971-90	1	134	[73]	
FR	1955-90	2	21	[63]	
UK	1986-96	1	112	[75]	
Total		23	734		

Table A3.3 summarises the literature on late ESRD in survivors of D+ HUS, from studies where the mean follow-up time was 10 years or more. There is one reference from Belgium and the Netherlands with 2/73 (2.7 %) late ESRD cases. Due to the low number of cases, there is considerable uncertainty in this estimate. Using additional data from other countries can reduce this uncertainty. The overall probability of late ESRD from international studies is 16/719 (2.2 %). These two estimates for the probability of late ESRD are not significantly different (Fisher's exact test). The longest reported follow-up of HUS patients was performed in Paris, France, with 4/76 late ESRD cases. The denominator in this estimate includes patients lost to follow-up, because it is likely that the hospital would have been consulted if these patients had developed ESRD. This study has also identified 4 additional patients who have developed chronic renal failure, more than 20 years after the initial episode of HUS. All these patients are expected to develop ESRD at some point of time, which may be 30 years or more after HUS. (M.F. Gagnadoux, Hopital Necker-Enfants-Malades, Paris, France; personal communication). Based on the data from Paris, 8/76 (10.5%) are expected to develop late ESRD uncertainty distribution $\pi_{E|H}$ ~ Beta (8,68). The French experience suggests that this hazard is experienced at least for 20 years, but it cannot be excluded that it extends beyond that period. The time to late ESRD varies from a few months to more than 20 years. To give an exact estimate of the probability and time to late ESRD, a meta-analysis of all available data should be undertaken. However, this requires access to individual patient records and is outside the scope of this study. We will approximate the time to late ESRD with a uniform distribution between 0 and 40 years (i.e. the probability to develop late ESRD per year of follow up is approximately 10.5% / 40 = 0.26%).

Table A3.3. Probability of late ESRD as a consequence of HUS

Country	**Period**	**late ESRD**	**HUS patients in follow-up**	**Reference**	**Comments**
NL	1965-77	2	73	[21]	Onset 11, 17 yr
USA	1979-88	2	50	[48]	
UK	1966-85	0	88	[30]	
Canada	1986-88	6	226	[66]	
USA	1971-90	2	133	[73]	Excludes two patients with ESRD after recurrent D-HUS
B	1970-82	0	73	[45]	
FR	1950-78	4	76	[33]	Onset 2 < 10 yr, 2 > 10 yr
Total		16	719		

Appendix 4 Clinical history of renal dialysis and transplantation

This Appendix summarises the analyses of the Renine database, aimed at obtaining parameter estimates for the waiting time to transplantation, the mortality rate for patients on dialysis in the first and later years, the case-fatality ratio of renal transplantation and the time to graft rejection. From the Renine database, information was extracted on patients with renal replacement therapy, who started dialysis in the period 1980 to 2000, with primary diagnoses Haemolytic Uraemic Syndrome, including Moschowitz Syndrome (code 88) and pyelonephritis (codes 20, 21, 22, 23, 24, 25 and 29). In the following, these diagnoses are abbreviated HUS and PYN, respectively. Patients were grouped in five age-categories, 0-15, 16-44, 45-65, 65-74 and 75+.

Time to tranplantation

The time to transplantation was first analysed by Kaplan-Meier analysis (SAS version 8.2, SAS Institute, Cary, NC, USA: Proc Lifetest). Differences between age or diagnostic groups were evaluated by the log-rank test with a critical p-value of 0.05. For both HUS and PYN, there were significant differences between age categories. There were no significant differences between HUS and PYN for any of the age categories. For the 75+ age group, only censored data were available. As transplantations in this age group are very rare, the data were combined with the 65-74 age group to create a 65+ group. A parametric analysis of the data was carried out by fitting a Weibull model (SAS Proc Lifereg). Goodness of fit was tested by comparing the predicted survival curve with the curve from the non-parametric KM analysis. The figures below show the observed data and the fitted models.

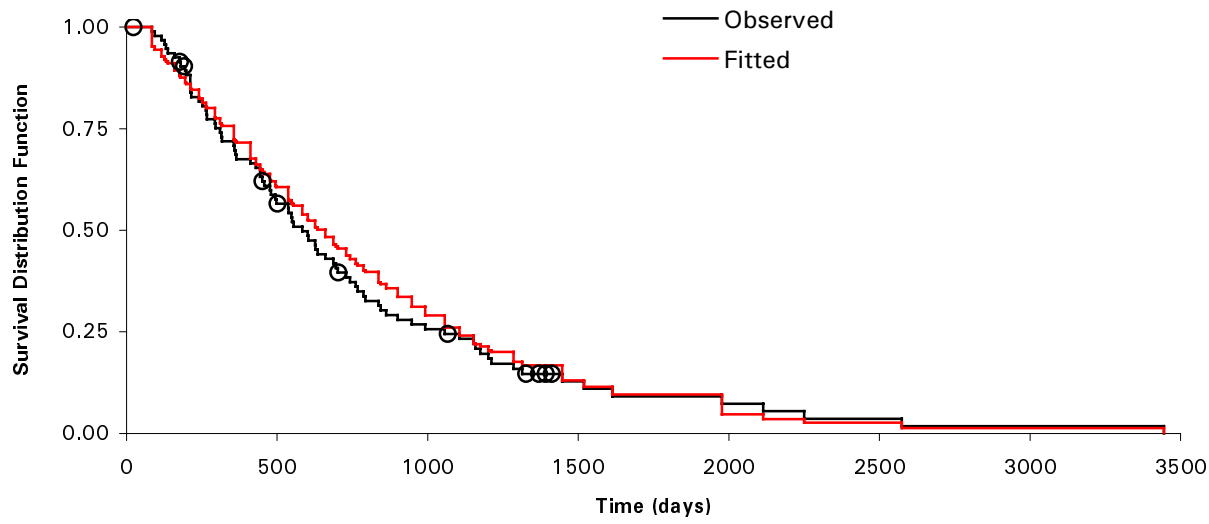

Figure A4. 1. Kaplan-Meier curves for time to transplantation, age group 0-15, diagnosis HUS and PYN (○ = censored data)

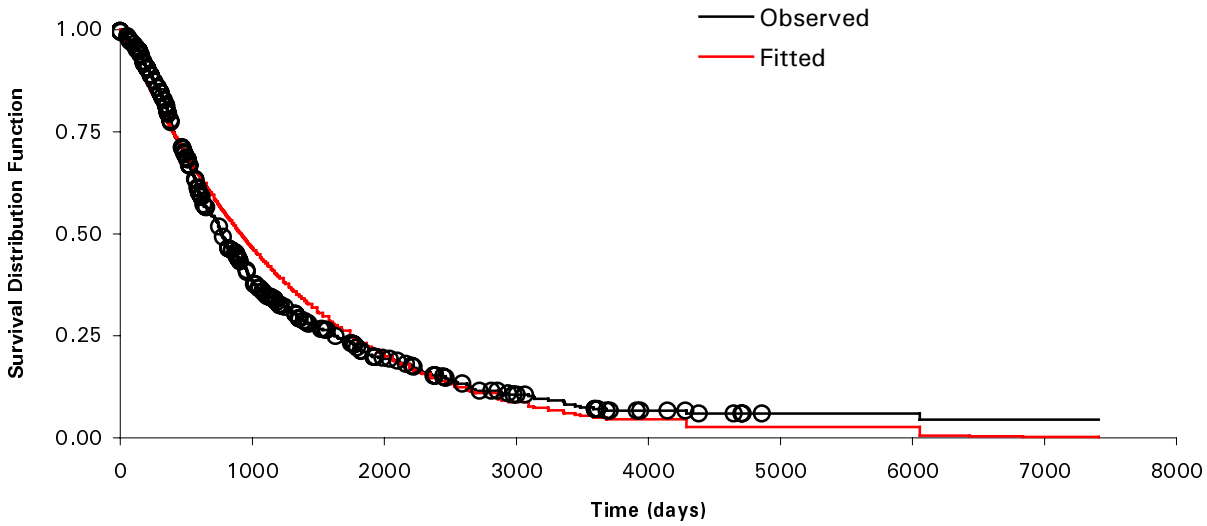

Figure A4. 2. Kaplan-Meier curves for time to transplantation, age group 16-44, diagnosis HUS and PYN (○ = censored data)

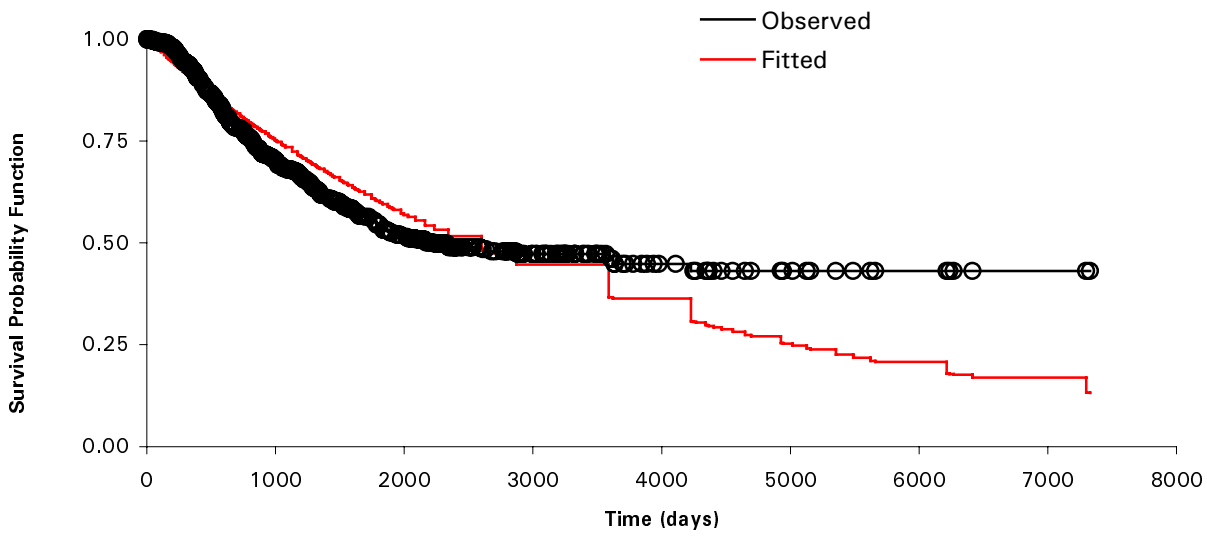

Figure A4. 3. Kaplan-Meier curves for time to transplantation, age group 45-64, diagnosis HUS and PYN (○ = censored data)

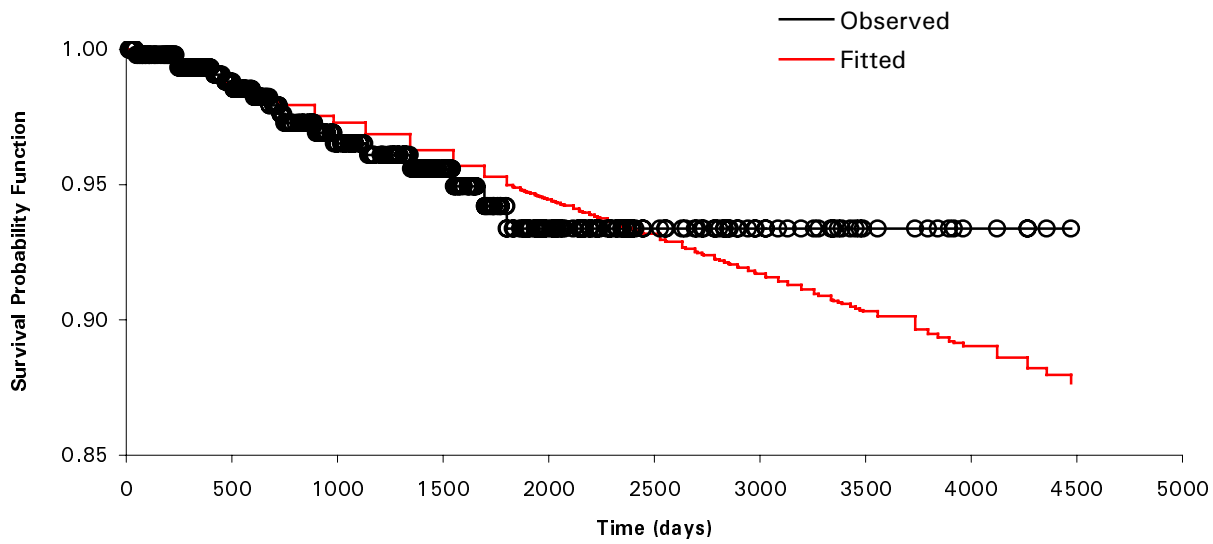

Figure A4. 4. Kaplan_Meier curves for time to transplantation, age group 65+, diagnosis HUS and PYN (○ = censored data)

The SAS Lifereg procedure fits a Weibull model of the form $S(t) = \Pr(T > t) = e^{-\alpha t^{\gamma}}$, where γ = 1/int and α = exp (-int / scale). To implement the Weibull model in @RISK, a transformation is necessary because @RISK uses a Weibull model of the form: $F(x) = 1 - e^{-\left(\frac{x}{b}\right)^{a}}$ (cumulative density function). It can be shown that for this form, a = 1/scale and b = exp(int).
The results of the survival analysis are as follows.

Table A4. 1. Parameters of fitted (SAS) Weibull models for time to transplantation, diagnosis HUS and PYN, different age groups

Age class	Int		Scale	
	Mean	Sem	Mean	Sem
0-15	6.74	0.086	0.763	0.062
16-44	7.16	0.041	0.936	0.031
45-64	8.18	0.067	1.017	0.048
65+	10.36	0.639	0.966	0.194

Sem: Standard error of the mean

Note that for the age class 0-15, the scale parameter is significantly lower than 1. This indicates that the probability of being transplanted increases when a patient is longer on the waiting list, which may be the consequence of active waiting list policy or the availability of living related donors. The scale parameter for other age classes does not differ significantly from 1, hence the waiting time could also be described by the simpler exponential distribution. For reasons of consistency, this simplification will not be made and all waiting times will be modelled with a Weibull distribution.
The transformed parameters, including conversion from days (the original input time scale) to years (the time scale for the simulation model) can then be computed as follows.

Table A4. 2. Parameters of Weibull (@RISK) simulation models for time to transplantation, diagnosis HUS and PYN, different age groups

Age class	@RISK simulation model		
	a	b (days)	b (years)
0-15	1.31	843	2.31
16-44	1.07	1280	3.51
45-64	0.98	3570	9.79
65+	1.04	31700	86.8

The Weibull models based on these parameter estimates represent the variability of waiting times in a population of patients. However, the parameters of the Weibull model are not known exactly, but with a margin of uncertainty. The SAS Lifereg procedure assumes a normal distribution for both int and scale and provides estimates of the standard error of the mean (see above). Samples from the distributions of int and scale can be used to explore the effects of uncertainty on the waiting time distributions. The figures below show, for each age class, 10 cumulative distributions of the variability of the waiting time. Each distribution was simulated using another independent sample of the distributions of int and scale.
The results show that the waiting time to transplantation increases considerably with age (see Table A4.3). The median waiting times computed from the Weibull model correspond well with the medians from the non-parametric Kaplan –Meier method. The high median value in the 65+ class suggests that it is uncommon for a patient in this age class to be eligible for transplantation, which is in accordance with the finding that only a few censored cases were observed in the 75+ age class. Inspection of the plot of cumulative distributions, and comparison of standard deviations between and within simulations, suggests that uncertainty is of minor importance for ages up to 64 years, but is of major importance for the 65+ age class.

Table A4. 3. Comparison of parametric (Weibull) and non-parametric (KM) results for time to transplantation, diagnosis HUS and PYN, different age groups

Age class	Median waiting time KM	Median waiting time Weibull	St. dev. between simulations	Pooled st. dev. within simulations
0-15	1.6	1.7	0.19	1.7
16-44	2.1	2.5	0.14	3.3
45-64	6.1	6.7	0.69	11
65+	NA	60	83	140

NA: not available

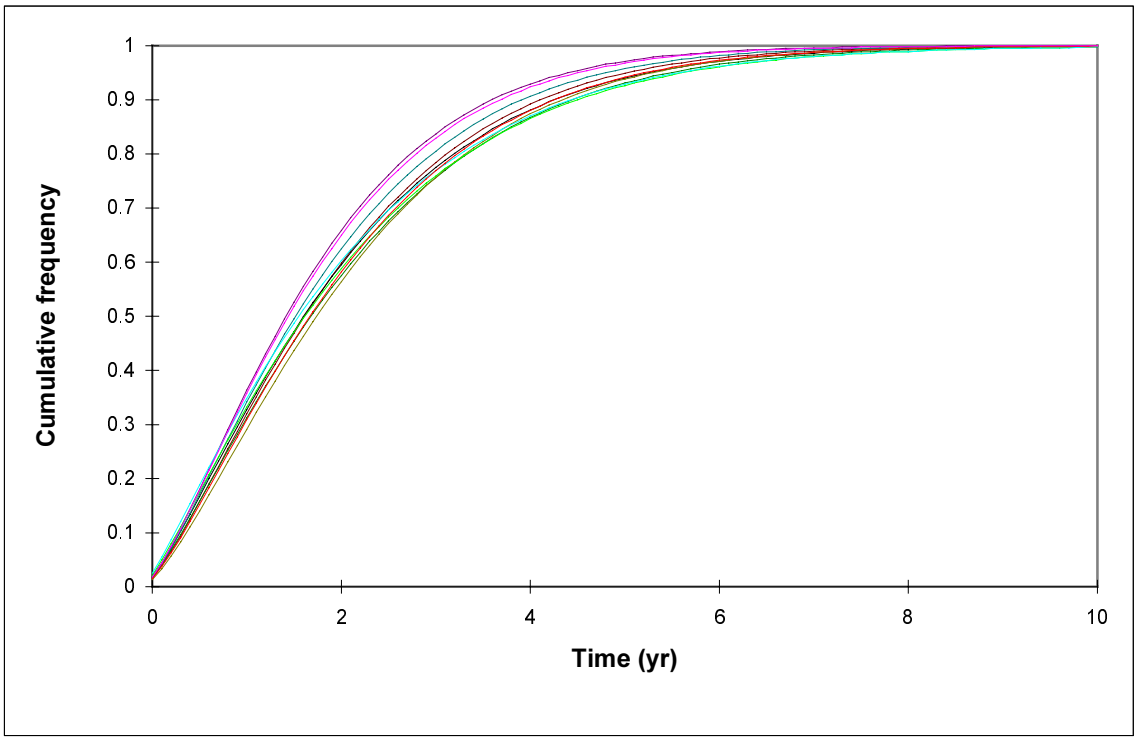

Figure A4. 5. Uncertainty in time to transplantation, age group 0-15

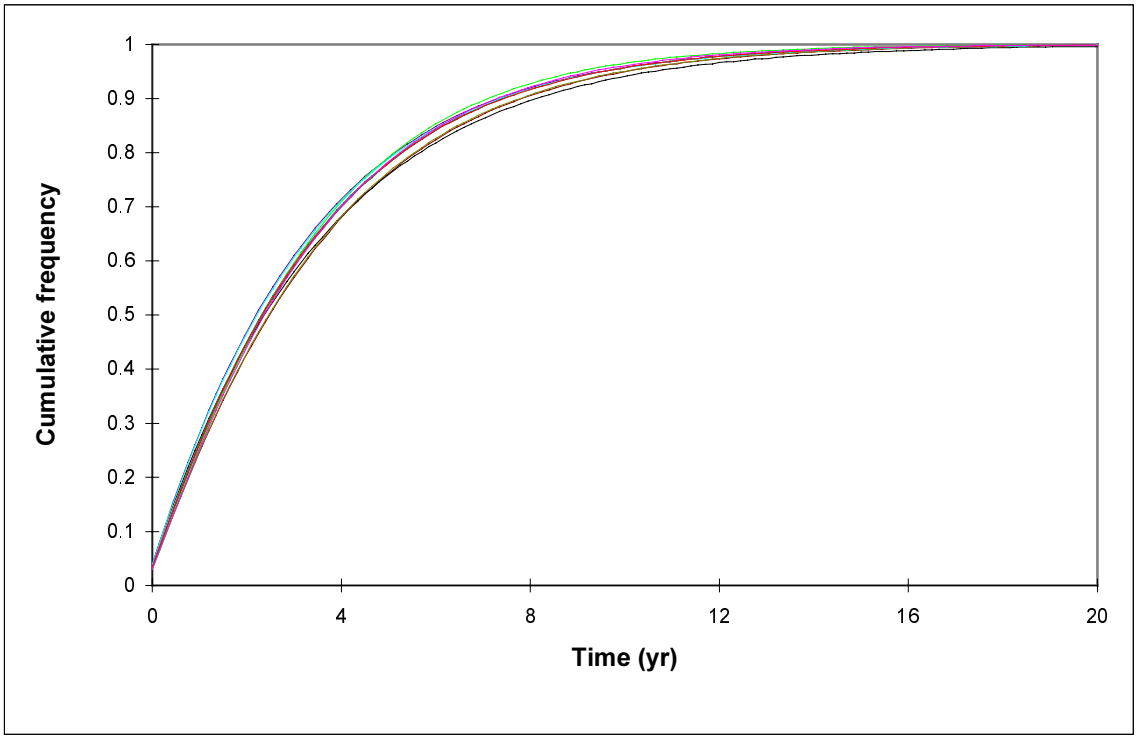

Figure A4. 6. Uncertainty in time to transplantation, age group 16-44, diagnosis HUS and PYN

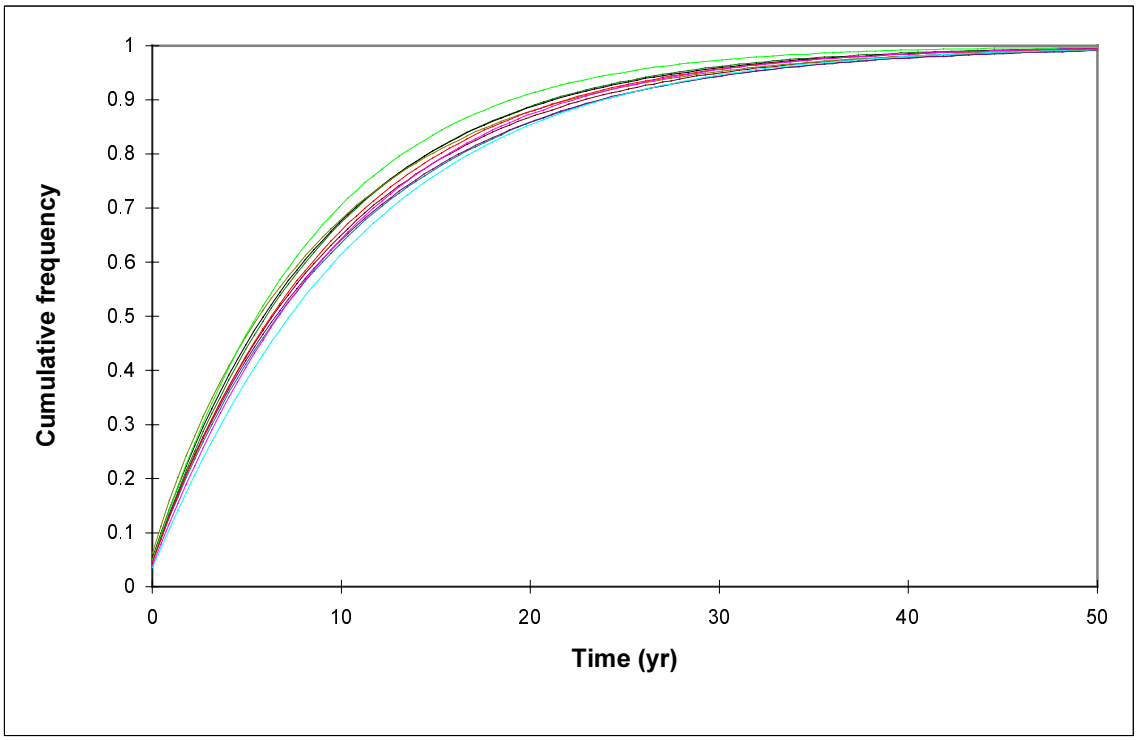

Figure A4. 7. Uncertainty in time to transplantation, age group 46-64, diagnosis HUS and PYN

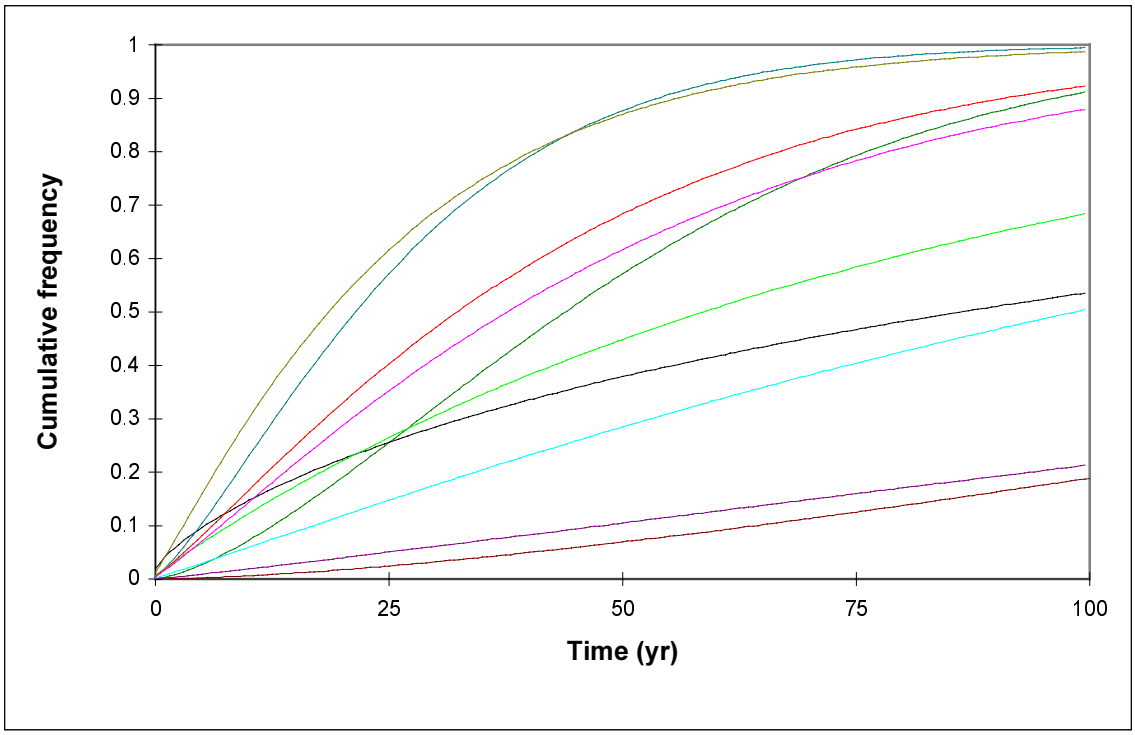

Figure A4. 8. Uncertainty in time to transplantation, age group 65+, diagnosis HUS and PYN

Time to graft failure

The time to graft failure was analysed according to the same strategy as time to transplantation. The Kaplan-Meier method demonstrated that there were significant differences between HUS and PYN patients in all age categories, hence pooling was not allowed. Within the HUS category, there were no significant differences between age groups. Therefore, all data for HUS patients were pooled and a Weibull model was fitted. Parameter values are shown in Table A4.4, the observed data and fitted model are illustrated in Figure A4.9.

Table A4. 4. Parameters of fitted (SAS) Weibull models for time to graft failure, diagnosis HUS, all ages

Age class	Int		Scale	
	Mean	Sem	Mean	Sem
All ages	8.07	0.352	2.13	0.282

Sem: Standard error of the mean

The scale parameter is significantly greater than one, indicating that the probability of graft rejection is greatest directly after the implantation. This is also obvious from the figure that clearly demonstrates that the greatest effects occur in the first 1000 days.

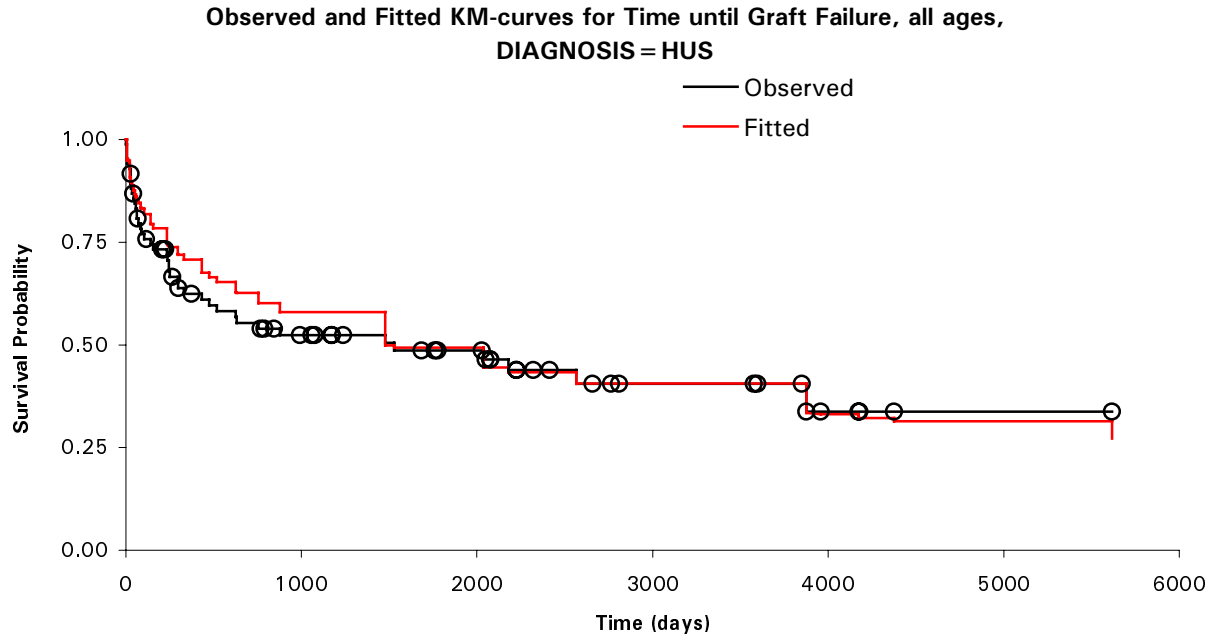

Figure A4. 9. Kaplan_Meier curves for time to transplantation, all ages, diagnosis HUS (○ = censored data)

The transformed parameters for the @RISK model are as follows.

Table A4. 5. Parameters of Weibull (@RISK) simulation models for time to transplantation, diagnosis HUS, all ages

Age class	@RISK simulation model		
	a	b (days)	b (years)
All ages	0.470	3200	8.75

The results of 10 simulations, using independent samples from the uncertainty distributions of the model parameters are shown in Figure A4.10.

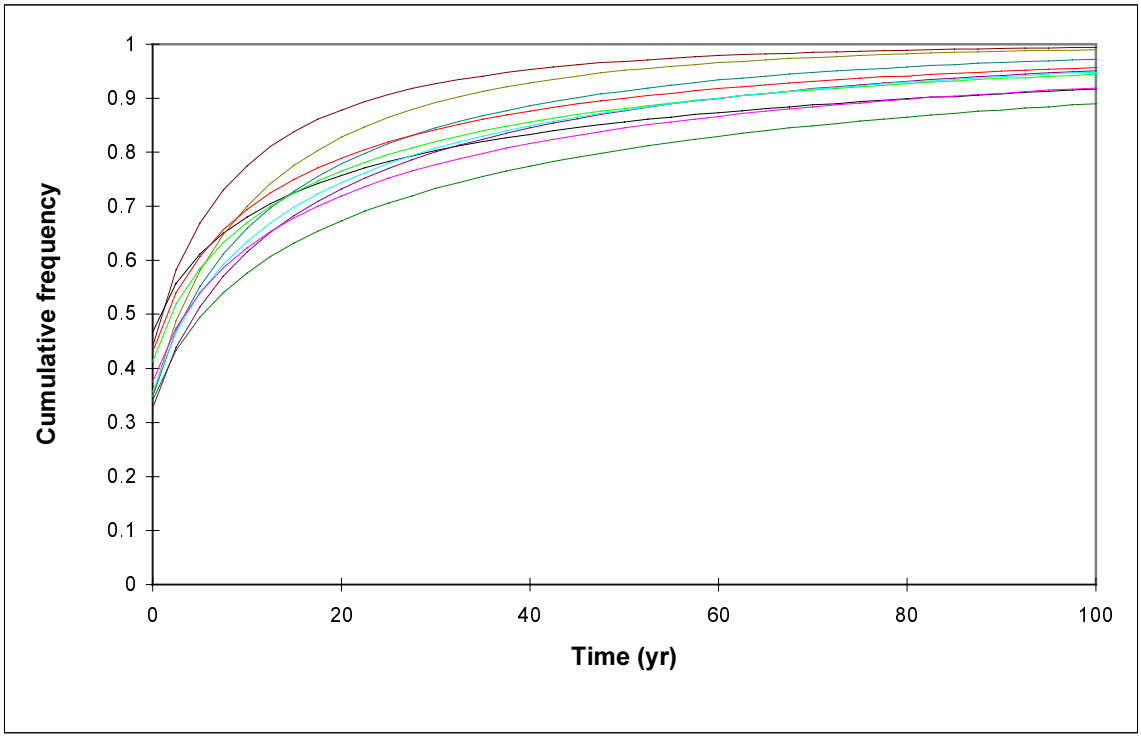

Figure A4. 10. Uncertainty in time to graft failure, all ages, diagnosis HUS

The results suggest that there is a fairly high probability of immediate graft rejection. However, this is an artefact related to the long time scale and consequent large time steps in the graph. A more detailed view of the first years after transplantation suggests that the probability of immediate graft rejection is less than 10%, whereas the probability of graft rejection within the first year varies between 20 and 35% (see Figure A4.11).
Median waiting times of the Weibull model and the non-parametric Kaplan-Meier method are similar as shown in Table A4.6. The standard deviation within simulations is larger than the standard deviation between simulations, but as can also be seen from the figures, the parameter uncertainty in not negligible.

Table A4. 6. Comparison of parametric (Weibull) and non-parametric (KM) results for time to transplantation, diagnosis HUS, all ages

Age class	Median waiting time KM	Median waiting time Weibull	St. dev. between simulations	Pooled st. dev. within simulations
All ages	4.2	4.0	12.3	72.8

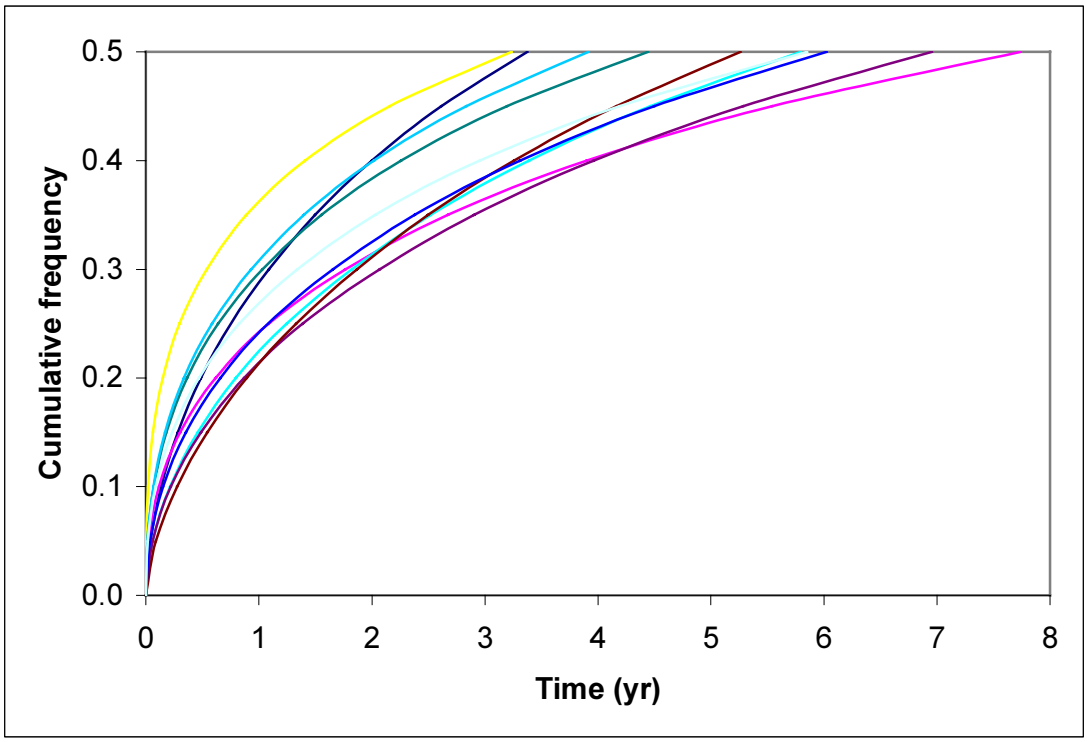

Figure A4. 11. Uncertainty in time to graft failure, all ages; diagnosis HUS, detail of Figure A4. 10

Mortality of dialysis patients

Visual inspection of the data indicated that the mortality of dialysis patients was higher in the first year than in later years. Therefore, two separate analyses were done. Table A4.7 shows the case-fatality ratios for the first year, by age class and diagnostic category.

Table A4. 7. Mortality in the first year after beginning dialysis

Age class	HUS			PYN			Pooled		
	N	Δ	π	N	Δ	π	N	Δ	π
0-15	17	0	0.00	25	2	0.08	42	2	0.05
16-44	35	7	0.20	168	11	0.07	203	18	0.09
45-64	9	3	0.33	154	58	0.38	163	61	0.37
65-74	4	2	0.50	121	79	0.65	125	81	0.65
75+	5	2	0.40	56	46	0.82	61	48	0.79

N: number of cases, Δ: number of deaths, π: case-fatality ratio,

Although there are some differences between the data for HUS and PYN, these are neither systematic nor very big, hence the pooled dataset will be used. The probability of dying in the first year increases significantly with age, from 5% in the 0-15 year old to 79% in the age group over 75 years. The uncertainty in the case-fatality ratio is quantified with beta distributions, e.g. for the 0-15 year old $\pi_{M|D}$ ~ Beta (2,40).

For illustration, the Figure A4.12 shows the uncertainty in the mortality risks in the first year after transplantation.

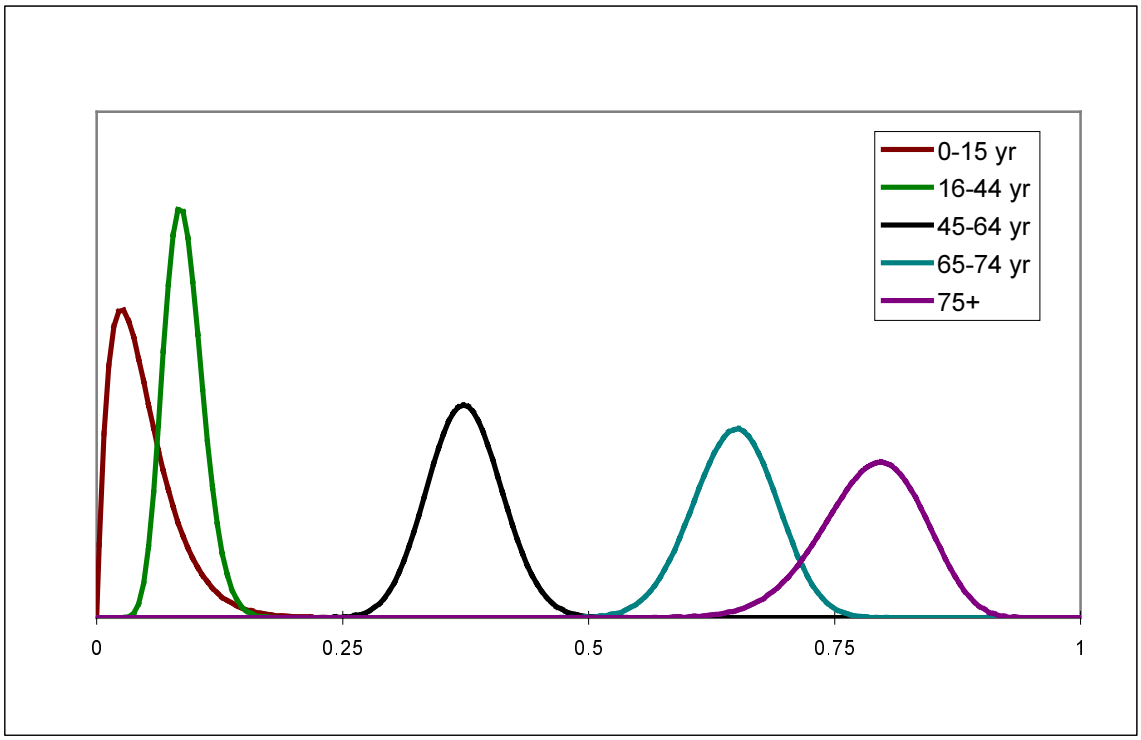

Figure A4. 12. Uncertainty in the risk of mortality in the first year after beginning dialysis, different age groups, diagnosis HUS and PYN

The estimated death rate for later years is based on observations from the second and third year of dialysis. Observations for later years were too few to provide additional information. We assume that after three years, no excess mortality occurs. Table A4.8 gives a summary of the available data. Note that the estimates, now calculated as the death rate per year, are considerably lower than in the first year and are not different from the death rates by all causes in the Netherlands. This indicates that after the first year, there is no significant excess mortality in dialysis patients.

Table A4. 8. Mortality in the second and third year after beginning dialysis

Age class	**HUS**		**PYN**		**Pooled**			**All causes**
	N	Δ	N	Δ	N	Δ	κ	Overall κ
0-15	16	0	62	0	77	0	0.000	0.003-0.006
16-44	66	3	524	13	590	16	0.015	0.003-0.016
45-64	33	8	523	88	555	96	0.085	0.016-0.133
65-74	0	0	337	123	337	123	0.185	0.133-0.327
75+	0	0	135	58	135	58	0.215	0.327-1.000

N: number of cases, Δ: number of deaths, κ: death rate (yr^{-1}) = Δ ./ (N x 2), Overall κ: death rate by all causes (men, the Netherlands, 1990-1995; Statistics Netherlands, 1998)

Mortality after renal transplantation

In the first year after transplantation, 3/39 HUS patients died. These fatalities are considered to be directly related to the transplantation, resulting in a mean case-fatality ratio of 7.7%, uncertainty distribution $\pi_{M|TX}$ ~ Beta (3, 36). No fatalities were observed in later years. The death rate among PYN patients was much higher, hence pooling is not allowed for these data.

Appendix 5 Severity weights for HUS and renal dialysis

To estimate severity weights for the clinical stage of HUS, we used the Euroqol-5D method. The effects of illness are characterised in five dimensions, with three levels each, see table. The distribution of patients over each level was based on clinical experience of dr. N. van de Kar (University Hospital Nijmegen, Department of Paediatrics). In the clinical phase, the illness has a strong effect on the well being of patients. Many blood samples are collected, a peritoneal catheter is introduced, renal replacement therapy is started and there is considerable psycho-emotional impact. After dismissal from the hospital, patients have recovered completely, there is only a very small chance of remission, and the quality of life is assumed to be normal so that the disease burden is only attributed to the clinical phase.

Table A5.1. Distribution of Euroqol states of HUS patients

Dimension	Level	HUS
Mobility	no problems in walking about	
	some problems in walking about	
	confined to bed	100%
Self-care	no problems with self-care	
	some problems with washing or dressing	
	unable to wash or dress	100%
Usual activities	no problems with performing usual activities	
	some problems with performing usual activities	
	unable to perform usual activities	100%
Pain/discomfort	no pain or discomfort	
	moderate pain or discomfort	25%
	extreme pain or discomfort	75%
Anxiety/depression	not anxious or depressed	
	moderately anxious or depressed	25%
	extremely anxious or depressed	75%

This information results in a distribution of patients over different Euroqol-5D scores, as described in table A6.2. The score was converted into a severity weight by the regression model of Dolan *et al*. [26]. This model produces a quality of life estimate on a scale which ranges from 1.000 for Euroqol-5D score 11111 to –0.594 for Euroqol-5D score 33333. To convert to a scale for use in calculating DALYs, the following conversion was made: “Severity weight”= (1 - “Dolan weight”) / 1.594.

Table A5.2. Distribution of severity weights for HUS patients

Euroqol score	Severity weight	Proportion of HUS patients
33322	0.731	6%
33323	0.835	19%
33332	0.896	19%
33333	1.000	56%

The Table and Figure below show the severity weight for dialysis, based on the study of De Wit et al. [22].

Table A5.3. Distribution of severity weights of dialysis patients

Severity weight	Frequency
0.000	33
0.074	11
0.094	4
0.096	1
0.117	9
0.118	2
0.128	8
0.139	1
0.151	8
0.162	4
0.172	3
0.173	1
0.182	2
0.194	10
0.196	3
0.216	1
0.238	1
0.239	4
0.260	3
0.304	1
0.323	3
0.345	1
0.367	1
0.388	1
0.400	2
0.433	1
0.445	2
0.457	1
0.465	1
0.505	1
0.510	1
0.548	1
0.565	1
0.574	2
0.611	1
0.619	1
0.639	1
0.675	2
0.683	1
Total	135

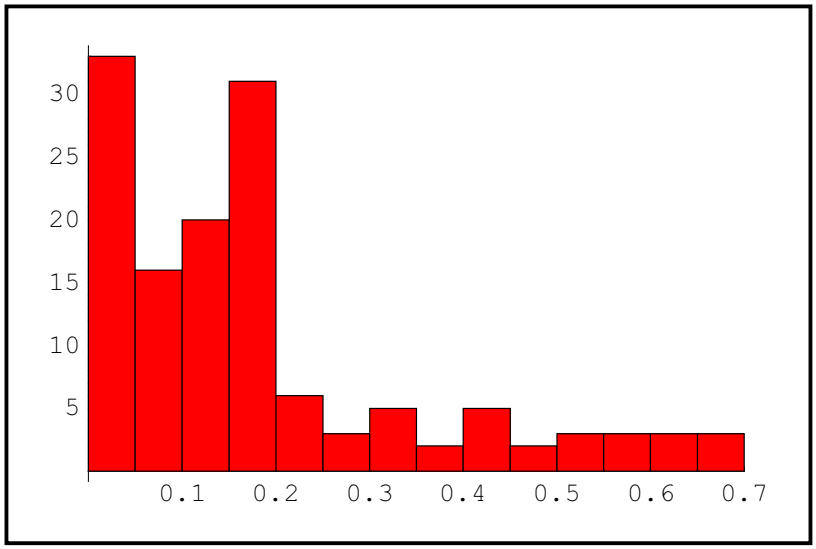

Figure A5.1. Distribution of severity weights of dialysis patients

Severity weights for renal transplantation and patients with functioning grafts were based on a German study. Greiner [37] followed 1023 patients on a waiting list until several years after eventual renal transplantation and converted EQ-5D scores in a tariff, comparable to that of Dolan as cited above, see Table. From these data, an average quality of life index of 0.82 can be calculated, which is equivalent to a severity weight of 0.18. We assume that the health

state after 14 months is representative for the quality of life with a functioning graft, i.e. severity weight 0.12. No data on variability were available. We therefore arbitrarily defined Beta distributions for this variability.

Table A5.4. Quality of life of patients after renal transplantation

Status of patient	**Quality of life index**
Waiting list	0.76
14 days after TX	0.73
1 month after TX	0.78
3 months after TX	0.82
6 months after TX	0.83
12 months after TX	0.86
14 or more months after TX	0.88

Appendix 6 Simulation of the variability in the individual life span as a function of age

Standard life tables, such as those published by Statistics Netherlands, provide only information on the average life expectancy at a given age. For the microsimulation as used in the HUS model, it was necessary to incorporate variability in the life-span of an individual. We based our model on published[8] age-specific mortality hazards, i.e. the probability of dying at age i, given survival to age i, see Figure A6.1. No difference between men and women was made, hazards were averaged over both sexes.

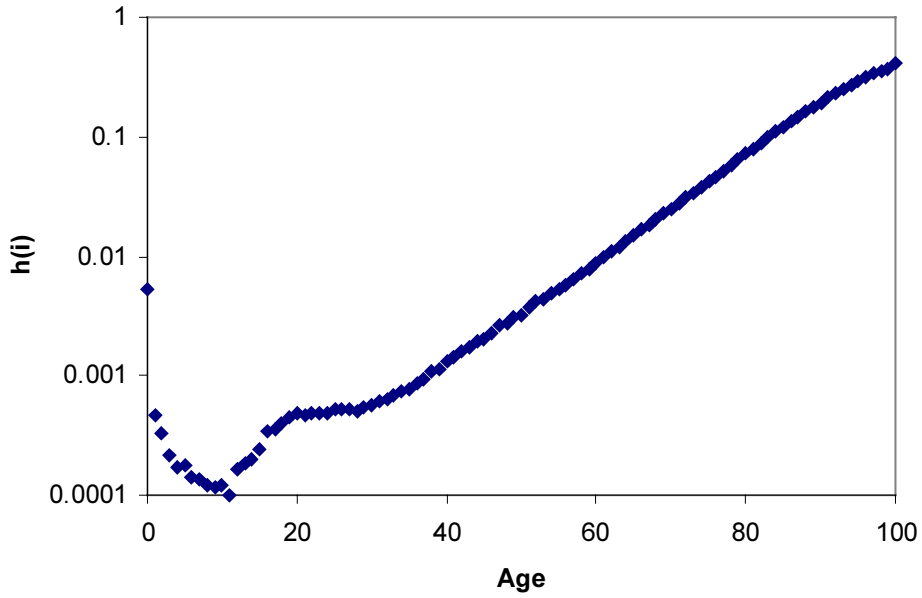

Figure A6.1. Mortality hazard h(i) for the Dutch population, 1996-2000

For a person of age i, a series of Bernoulli trials was simulated to model the expected age at death. The exact moment of death was then modelled by addition of a sample from a Uniform (0,1) distribution.

S (i+1) = Bernoulli (h(i));
if S(i+1) = 0, S (i+2) = Bernoulli (h(i+1)),
else e(i) = i + Uniform (0,1);
if S(i+2) = 0, S (i+3) = Bernoulli (h(i+2)),
else e(i) = i+1+ Uniform (0,1);
etc.

In one iteration of the model, a series of Bernoulli trials was simulated for one individual of each age between 0 and 99 years, all individuals at age 100 were supposed to die in the next year. Hence, each iteration produced a set of expected life spans for all ages between 0 and 100 years. Figure A6.2 shows the results of the simulation.

[8] CBS Statline, data for 1996-2000

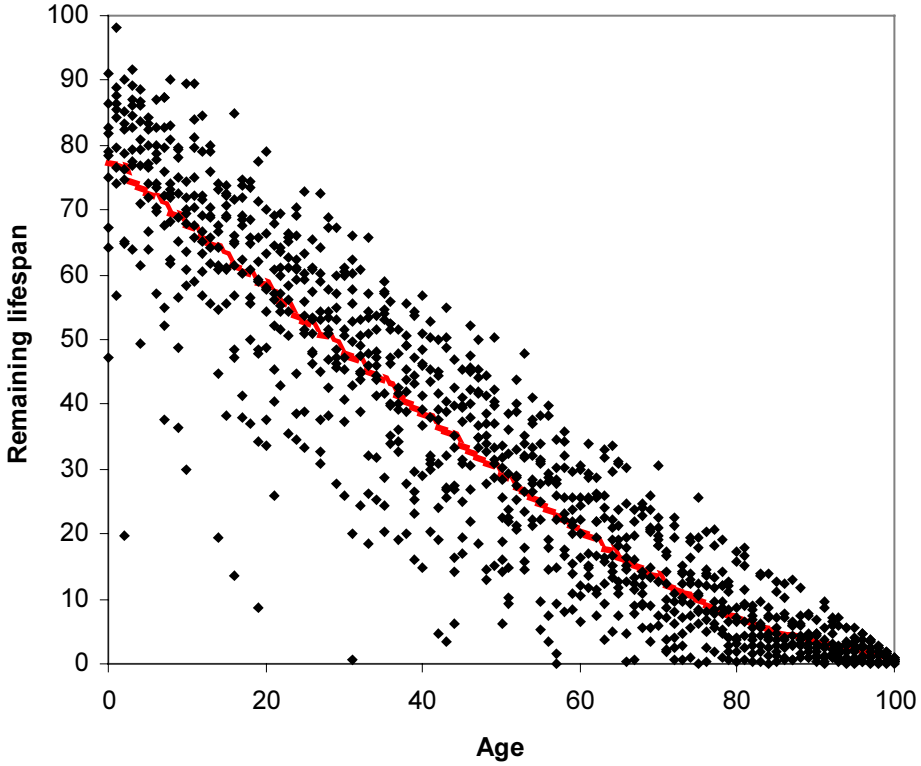

Figure A6.2. Expected individual life span of the Dutch population, 1996-2000.
red line: mean of 1000 samples, diamonds: 10 samples from the variability distribution for each age

The model was validated by comparison of the average of simulated individual life spans (the red line if Figure A6.2) with the analytical life expectancy as published by Statistics Netherlands, see Figure A6.3. The graph shows that the difference between both methods varies randomly and is less than +/-0.5 years for all ages except 100 years. The latter is related to our assumption that all individuals die in their 101st year of life.

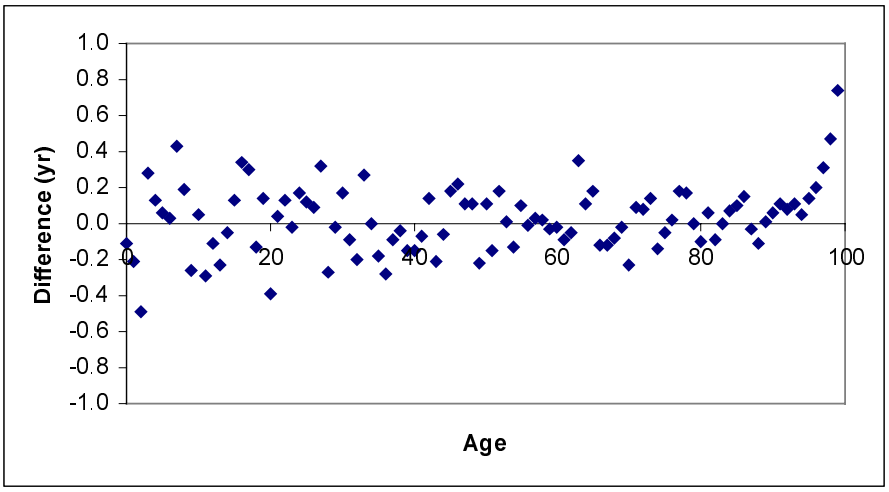

Figure A6.3. Validation of stochastic model for expected individual life span

Appendix 7 Stability of the simulation model

This Appendix gives some technical details on the numerical stability of the simulation model.

Number of iterations per simulation

To determine the necessary number of iterations for each simulation, the model was run with all uncertain parameters set at their median value. In total, 5000 iterations were performed. The figures show trails for the running mean, median, standard deviation and 5- and 95-percentile for Total DALY, Total YLL and Total YLD. The table shows the maximum change in the 95-percentile after 1000, 1500 and 2000 iterations. The results demonstrate that already after 1000 iterations a relatively stable result is obtained. To allow for some more variation when input parameters are at more extreme values than their mean, a choice was made for 1500 iterations per simulation in the final model runs.

Table A7.1. Numerical stability of simulation results, variation of the number of iterations

# iterations	Maximum change in 95-percentile		
	DALY	YLL	YLD
1000	0.72%	0.50%	2.39%
1500	0.72%	0.50%	1.69%
2000	0.72%	0.50%	0.88%

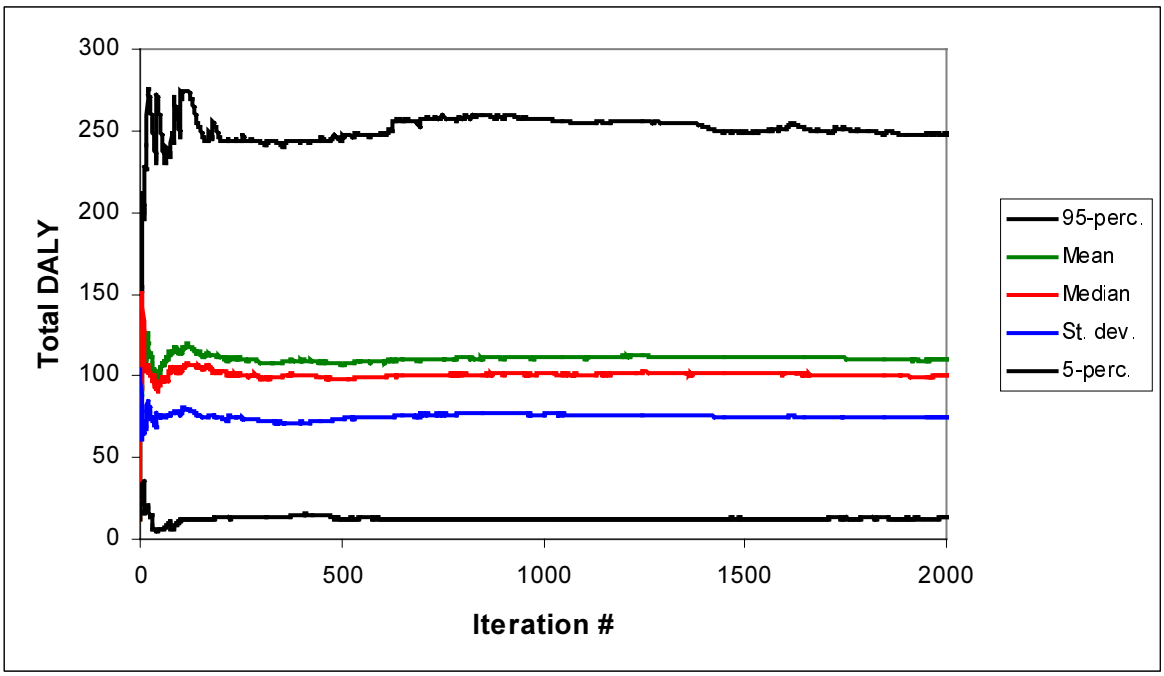

Figure A7.1. Trails for running mean, median, 5- and 95-percentiles (upper panel) and change in the 95-percentile (lower panel) of total DALY

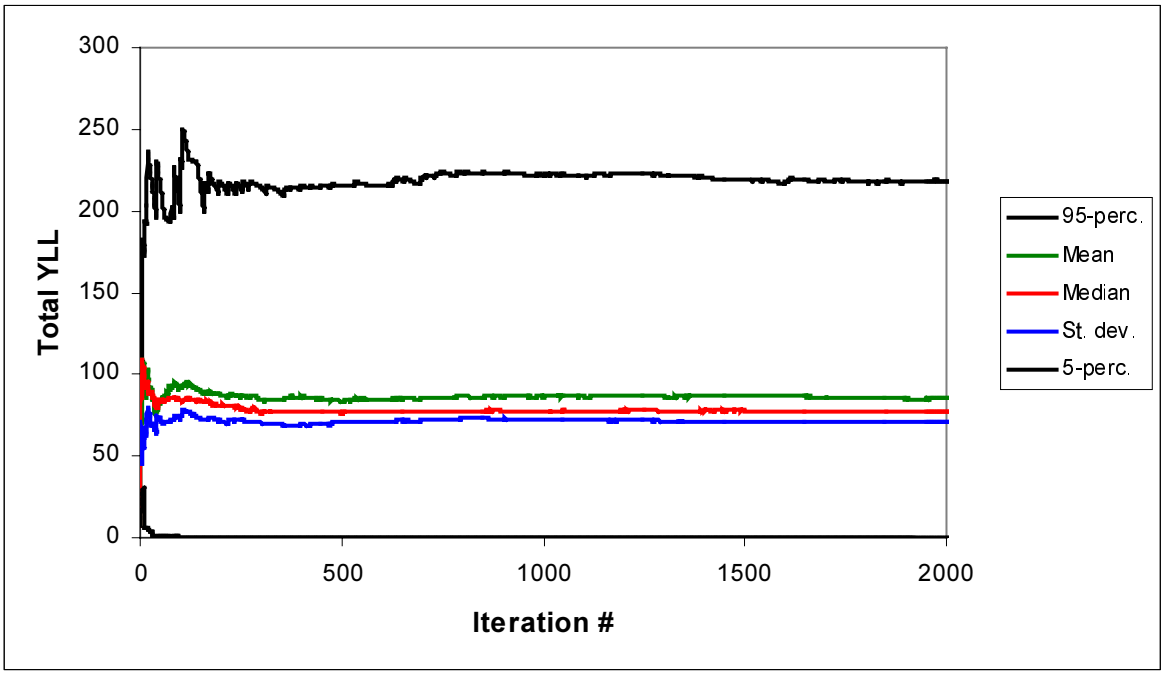

Figure A7.2. Trails for running mean, median, 5- and 95-percentiles (upper panel) and change in the 95-percentile (lower panel) of total YLL

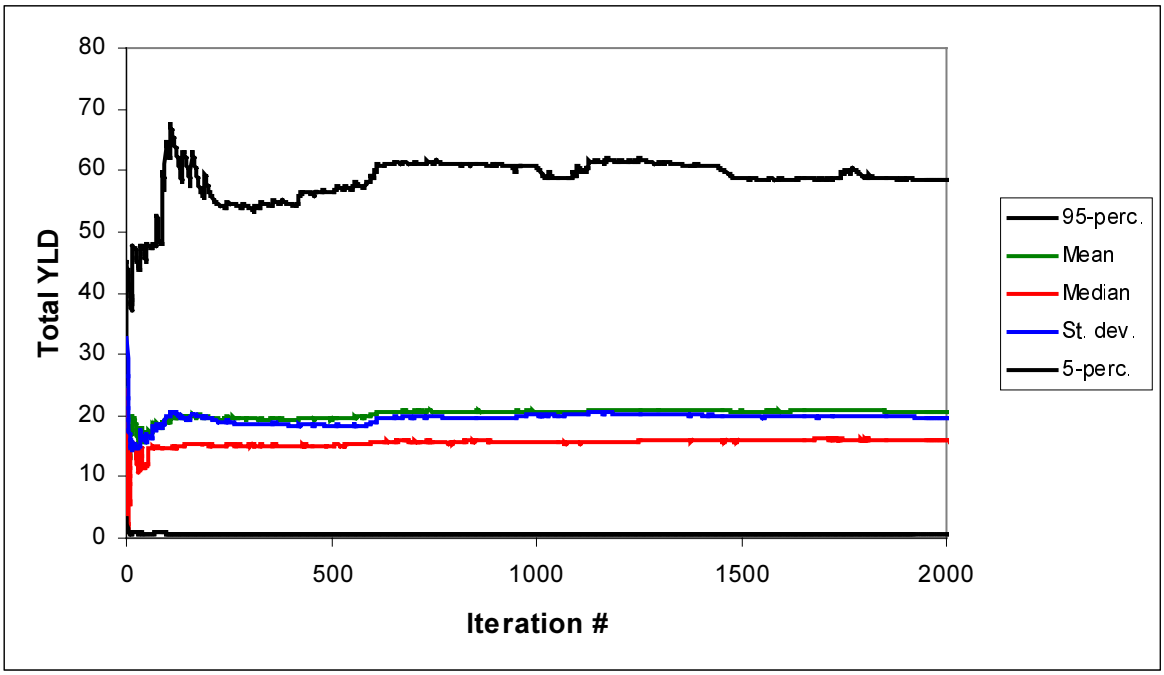

Figure A7.3. Trails for running mean, median, 5- and 95-percentiles (upper panel) and change in the 95-percentile (lower panel) of total YLD

Number of simulations per model run

To determine the necessary number of simulations for each model, the complete model was calculated with Latin Hypercube samples from the uncertain parameters. In total, 250 simulations were performed. The figures show trails for the running mean, median, standard deviation and 5- and 95-percentile for Mean and Standard Deviation of Total DALY, Total YLL and Total YLD, and also the change in the 95-percentile of these output values. The table shows the maximum change in the 95-percentile after 100 and 250 simulations. The results demonstrate that already after 200 simulations a relatively stable result is obtained. It was therefore decided to perform 250 simulations per model run.

Table A7.2. Numerical stability of simulation results, variation of the number of simulations (of 1500 iterations each)

# simulations	**Maximum change in 95-percentile of the mean**		
	DALY	YLL	YLD
100	2.3%	3.4%	6.6%
200	0.6%	1.1%	1.3%

# simulations	**Maximum change in 95-percentile of the standard dev.**		
	DALY	YLL	YLD
100	0.7%	0.5%	4.0%
200	0.3%	0.4%	4.0%

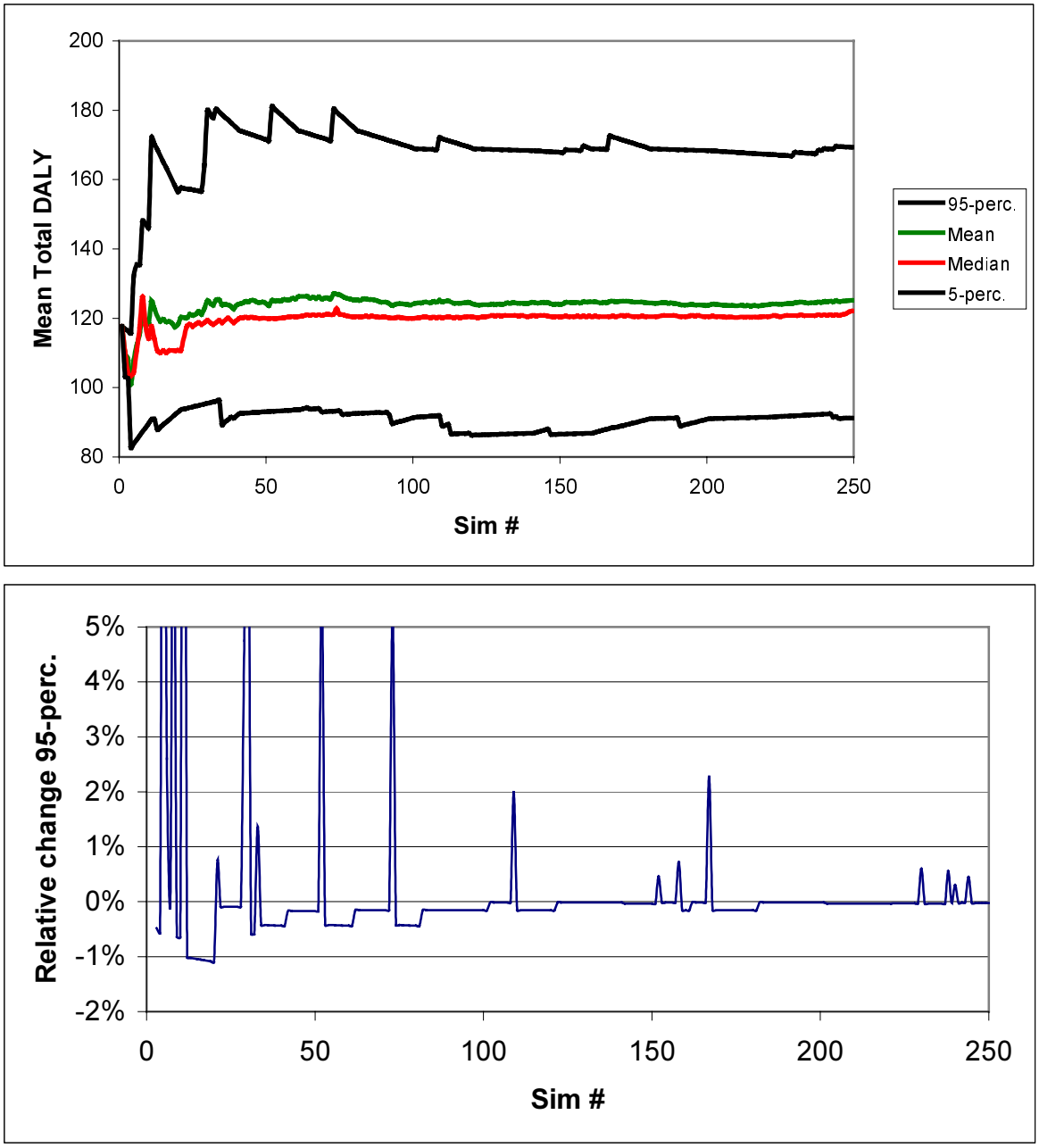

Figure A7.4. Trails for running mean, median, 5- and 95-percentiles (upper panel) and change in the 95-percentile (lower panel) of mean of total DALY

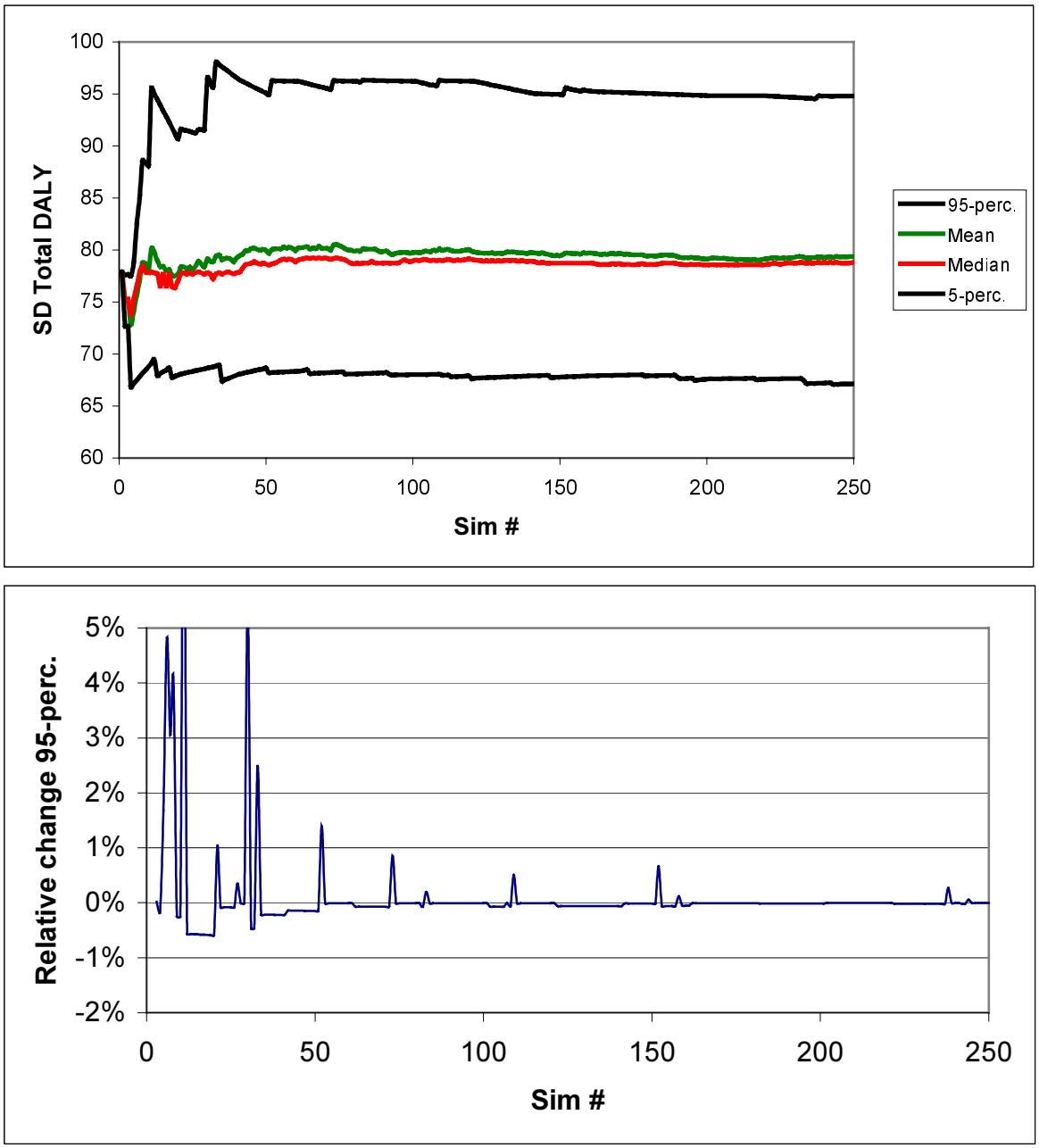

Figure A7.5. Trails for running mean, median, 5- and 95-percentiles (upper panel) and change in the 95-percentile (lower panel) of the standard deviation of total DALY

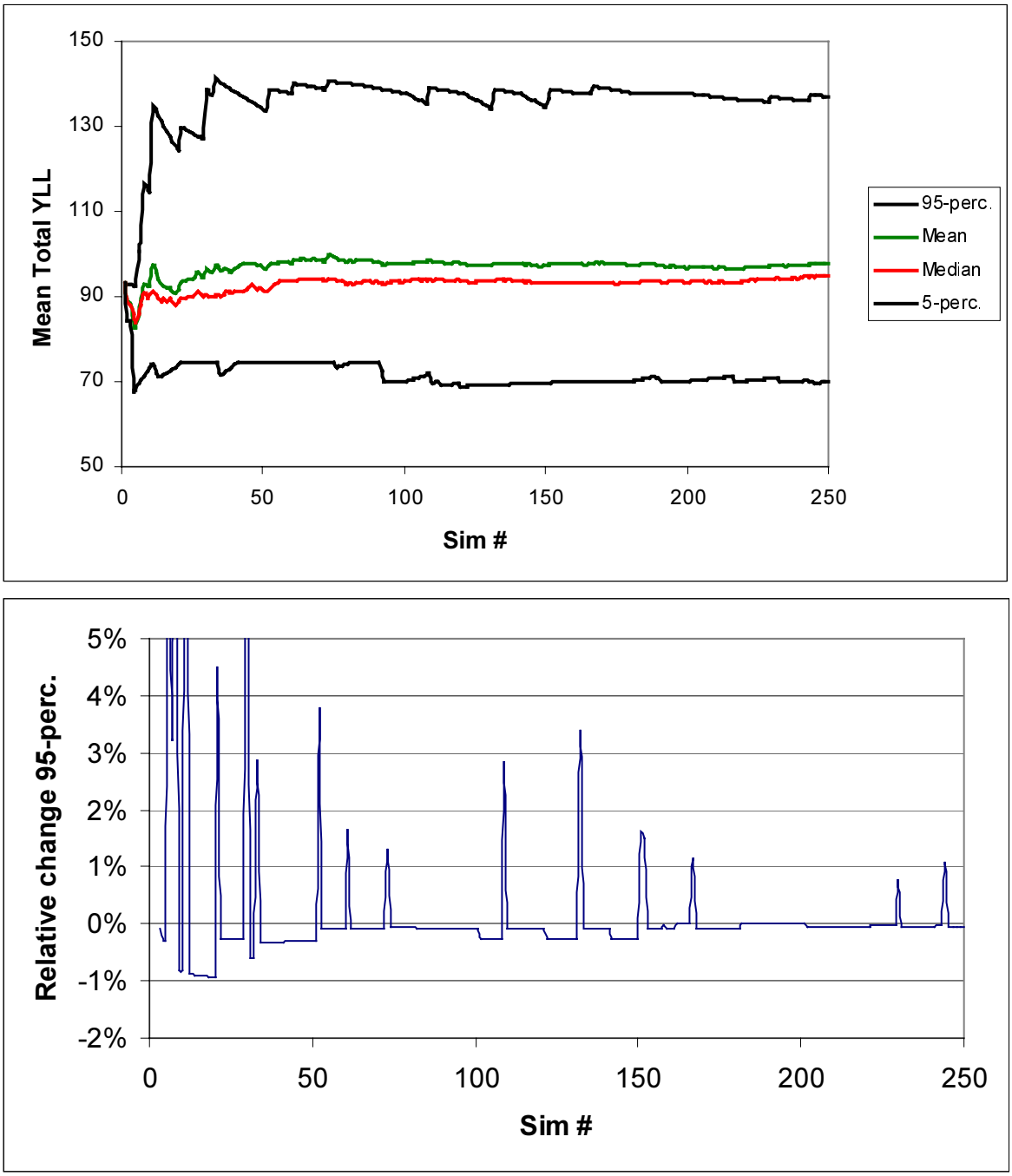

Figure A7.6. Trails for running mean, median, 5- and 95-percentiles (upper panel) and change in the 95-percentile (lower panel) of mean of total YLL

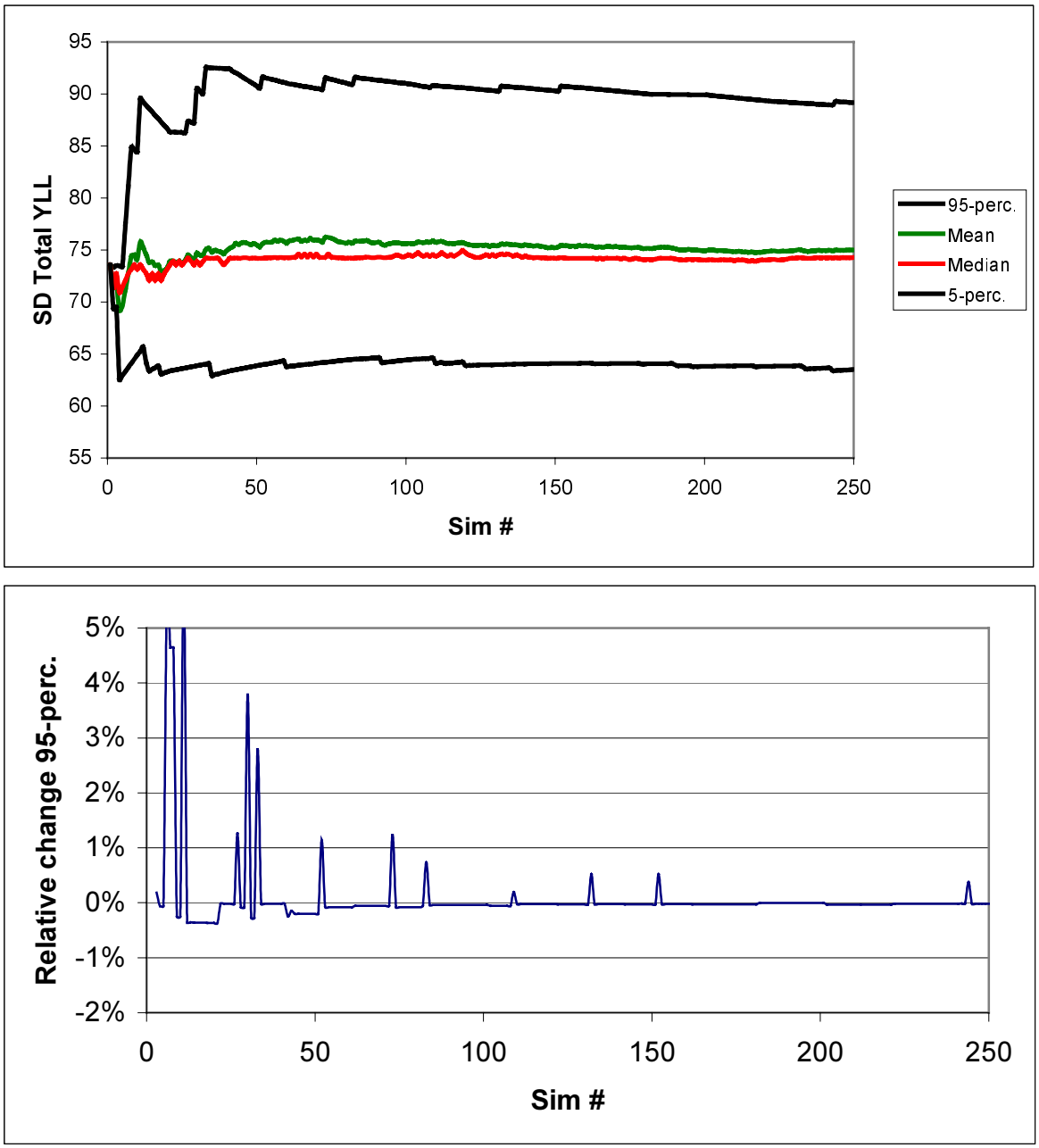

Figure A7.7. Trails for running mean, median, 5- and 95-percentiles (upper panel) and change in the 95-percentile (lower panel) of the standard deviation of total YLL

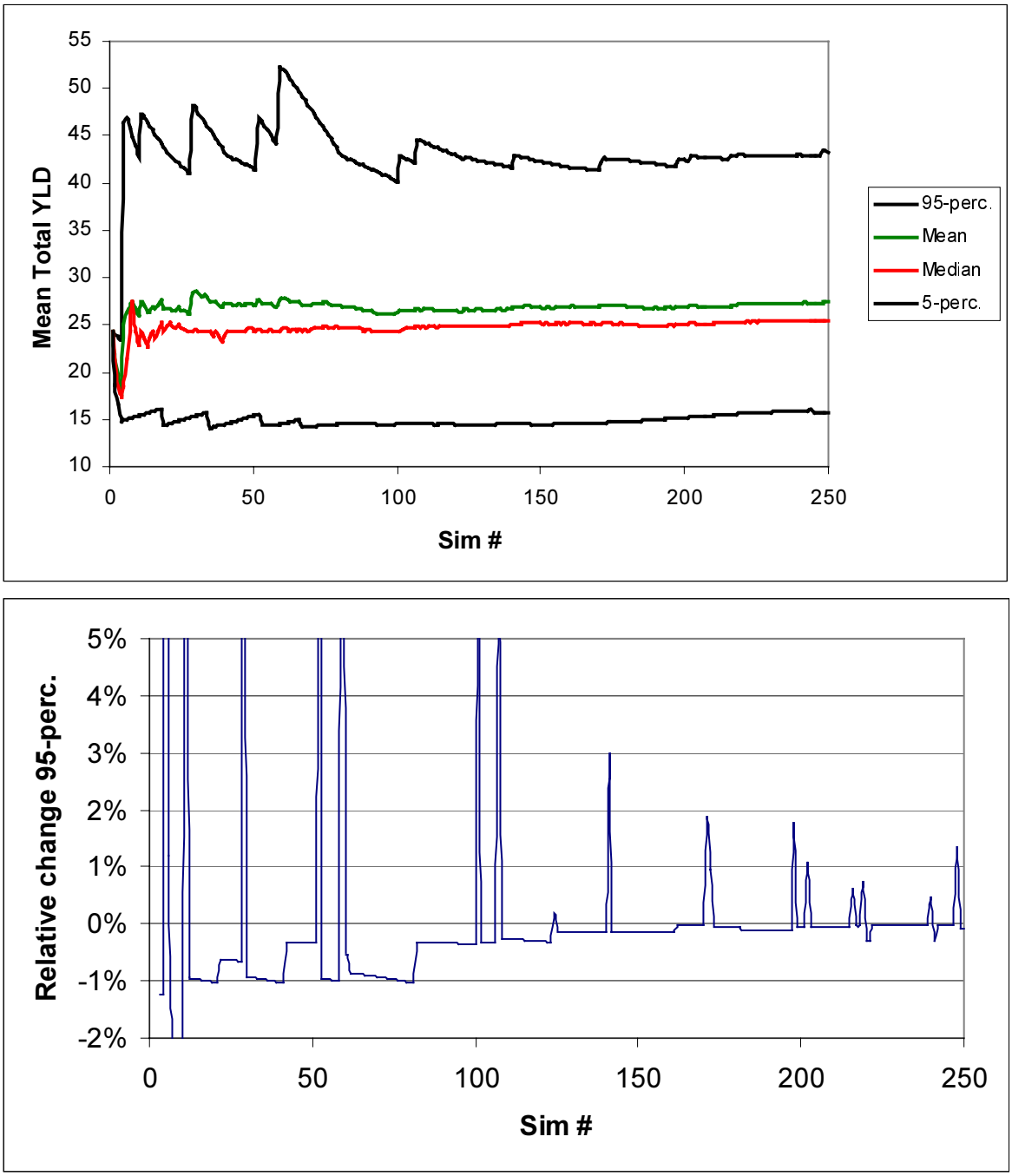

Figure A7.8. Trails for running mean, median, 5- and 95-percentiles (upper panel) and change in the 95-percentile (lower panel) of mean of total YLD

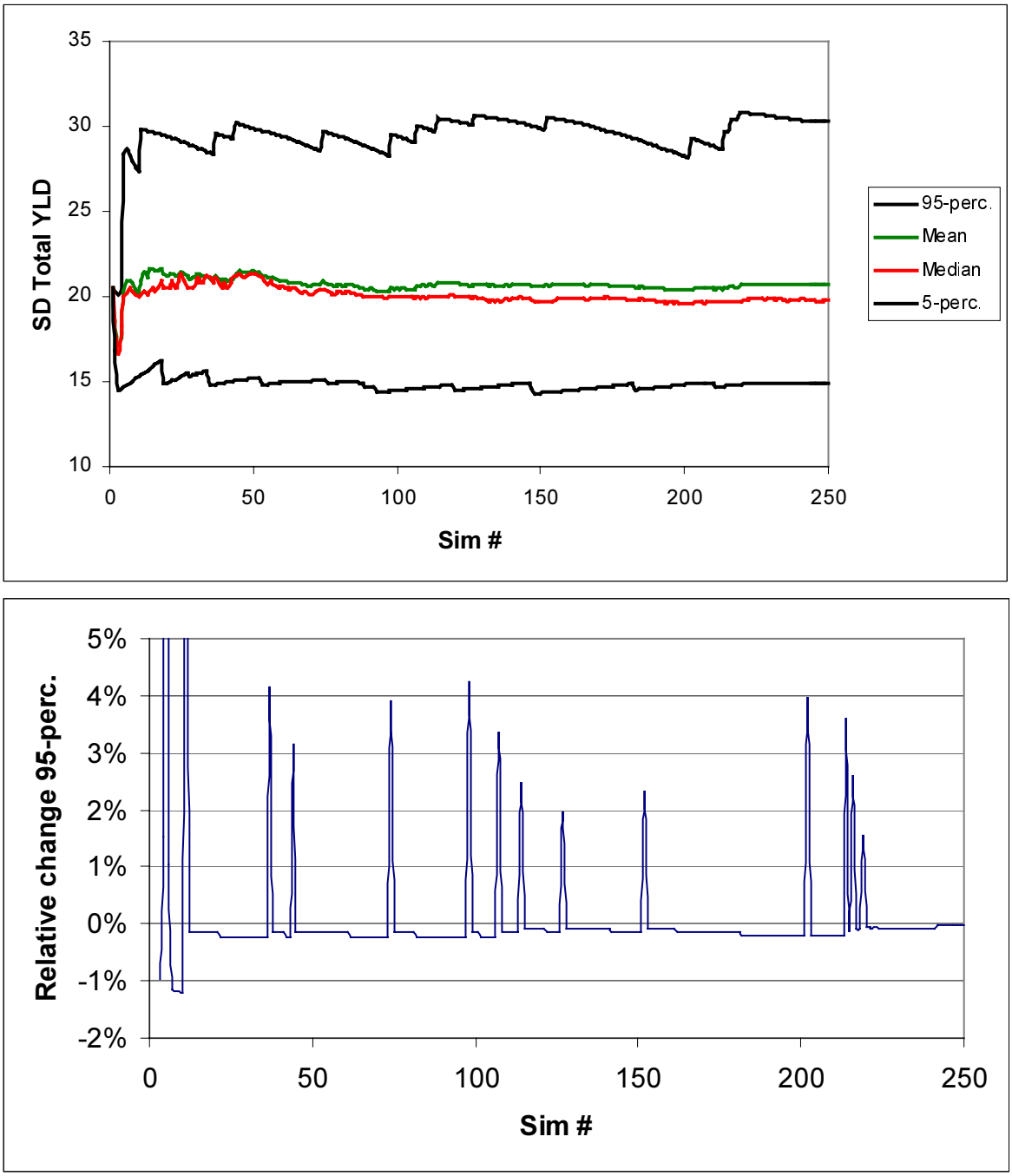

Figure A7.9. Trails for running mean, median, 5- and 95-percentiles (upper panel) and change in the 95-percentile (lower panel) of the standard deviation of total YLD

Appendix 8 Statistics of output distributions

Output parameter	Means							Median
	Mean	SD unc	SD var	F var/unc	5-perc.	Median	95-perc.	Median
Total GE / Incidence	2114	2641	39.65	0.00023	98	1288	6796	1288
Total GE / YLD	6.7	8.2	0.149	0.00033	0.3	4.1	21.0	4.1
Total GE / YLL	7.4	5.5	13.82	6.2	1.3	6.0	17.7	0.0
Total GE / DALY	14.0	9.3	13.82	2.2	3.5	12.7	30.6	6.1
HUS / Incidence	21.6	3.9	6.338	2.6	16.4	21.2	29.1	21.0
HUS / Incidence < 15	15.3	1.3	3.934	9.3	13.2	15.4	17.3	15.0
HUS / Incidence >= 15	6.4	3.6	3.393	0.89	2.1	5.5	13.1	5.0
HUS / YLD	1.0	0.2	0.308	3.6	0.8	1.0	1.3	1.0
HUS / Mortality	2.2	1.0	1.639	2.8	1.1	2.0	4.2	2.0
HUS / Mortality < 65	0.7	0.2	0.863	30.0	0.5	0.7	1.0	1.0
HUS / YLL	57.8	12.7	61.03	23.1	40.3	56.3	80.5	34.9
HUS / DALY	58.8	12.8	61.06	22.7	41.1	57.2	81.8	36.1
Incidence ESRD / Immediate	0.6	0.2	0.753	25.2	0.3	0.5	0.8	0.0
Incidence ESRD / Late	2.0	0.8	1.414	3.5	1.0	1.9	3.4	2.0
First dialysis period / Incidence	2.5	0.8	1.615	4.0	1.5	2.5	4.1	2.0
First dialysis period / YLD	4.0	1.3	4.687	12.3	2.1	3.8	6.5	2.3
First dialysis period / Mortality	0.08	0.03	0.282	69.4	0.04	0.08	0.14	0.00
First dialysis period / YLL	4.0	1.7	15.07	83.1	1.8	3.7	6.8	0.0
First dialysis period / DALY	8.0	2.8	15.87	32.3	4.1	7.6	12.9	2.5
First transplantation / Incidence	2.1	0.6	1.447	5.5	1.3	2.1	3.3	4.0
First transplantation / YLD	0.4	0.1	0.253	6.1	0.2	0.3	0.6	0.4
First transplantation / Mortality	0.2	0.1	0.386	11.4	0.0	0.1	0.4	0.0
First transplantation / YLL	8.9	6.0	22.51	14.0	1.8	7.8	19.8	0.0
First transplantation / DALY	9.2	6.0	22.51	13.9	2.3	8.1	20.2	0.4
Life with healthy graft / Incidence	2.0	0.6	1.386	5.9	1.2	1.9	3.1	2.0
Life with healthy graft / YLD	3.0	1.0	3.83	14.1	1.5	2.9	4.8	1.1
Dialysis after GR1 / Incidence	1.7	0.5	1.298	6.7	1.0	1.7	2.7	1.0
Dialysis after GR1 / YLD	3.3	1.8	11.37	41.7	1.3	2.9	6.6	0.5
Dialysis after GR1 / Mortality	0.07	0.03	0.263	99.3	0.04	0.07	0.12	0.00
Dialysis after GR1 / YLL	3.0	1.1	12.3	129	1.4	2.9	4.8	0.0
Dialysis after GR1 / DALY	6.3	2.4	17.71	53.0	3.3	5.8	10.5	0.6
Second transplantation / Incidence	1.5	0.4	1.216	8.1	0.9	1.5	2.4	1.0
Second transplantation / YLD	0.3	0.1	0.214	8.6	0.1	0.2	0.4	0.2
Second transplantation / Mortality	0.1	0.1	0.327	20.2	0.0	0.1	0.2	0.0
Second transplantation / YLL	5.4	3.3	16.91	25.9	1.6	4.8	11.3	0.0
Second transplantation / DALY	5.7	3.3	16.91	25.7	1.9	5.1	11.7	0.2
Life with healthy graft / Incidence	1.4	0.4	1.173	8.4	0.8	1.4	2.2	1.0
Life with healthy graft / YLD	2.0	0.6	3.077	23.8	1.1	1.9	3.1	0.4
Dialysis after GR2 / Incidence	1.2	0.4	1	9.0	0.7	1.2	1.9	1.0
Dialysis after GR2 / YLD	8.8	2.6	12.22	22.0	5.0	8.4	13.7	3.3
Dialysis after GR2 / Mortality	0.02	0.01	0.155	278	0.01	0.02	0.04	0.00
Dialysis after GR2 / YLL	0.2	0.1	1.85	1111	0.1	0.2	0.3	0.0
Dialysis after GR2 / DALY	8.9	2.6	12.44	22.1	5.0	8.5	14.0	3.4
Total HUS / YLD	22.7	6.3	21.75	11.8	13.6	22.5	34.7	17.6
Total HUS / YLL	79.2	18.0	70.2	15.2	56.9	76.2	111.6	69.4
Total HUS / DALY	101.9	21.4	74.97	12.3	74.4	98.3	141.3	87.5
Total GE and HUS / YLD	29.4	10.3	21.75	4.4	16.7	27.4	47.9	22.7
Total GE and HUS / YLL	86.6	18.9	72.06	14.5	62.5	83.6	122.6	75.2
Total GE and HUS / DALY	115.9	23.3	76.62	10.8	84.9	113.1	158.5	101.8

The first seven data columns give summary statistics of the means per simulation, the last column give the median of the medians per simulation; GR: graft rejection