Estimating the Costs and the Disease Burden Associated With Campylobacter Infections and Sequelae in The Netherlands

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ESTIMATING THE COSTS AND THE DISEASE BURDEN ASSOCIATED WITH CAMPYLOBACTER INFECTIONS AND SEQUELAE IN THE NETHERLANDS

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Abstract

Campylobacter infections pose an important public health problem in the Netherlands. Approximately 79,000 persons per year are estimated to experience symptoms of acute gastroenteritis. Further annually some 1400 ReA cases, 60 GBS cases and 11 IBD cases are associated with a previous Campylobacter infection. Using a stochastic simulation model the disease burden and the cost-of-illness of Campylobacter infections and its sequelae were estimated. Estimates of the Campylobacter-associated disease burden and costs-of-illness were 1185 DALYs (90% C.I. 693 – 1845 DALYs) per year and some 21 million € (90% C.I. 10 - 38 million €) per year respectively.

Keywords: Campylobacter; sequelae; cost-of-illness; disease burden; the Netherlands

1. Introduction

Campylobacter infections in humans cause acute gastro-enteritis (GE), which, in most cases, is self-limiting within a few days to weeks. For some patients the disease is fatal. Guillain-Barré Syndrome (GBS), reactive arthritis (ReA) and inflammatory bowel disease (IBD) are the most significant sequelae occurring occasionally after campylobacteriosis. Human Campylobacter infections pose an important public health problem in the Netherlands.

With the availability of a more recent Dutch epidemiological study with a much lower estimated annual number of GE cases than in a study carried out in the earlier nineties, an update of the previous estimate of the disease burden associated with Campylobacter infections and sequelae in the Netherlands of Havelaar *et al.* (2000a, b) was necessary. This was the first objective of the current study. Given that there is no estimate of the cost-of-illness associated with Campylobacter infections and the consequences of its sequelae for the Dutch society, the second objective of this study was to estimate the cost-of-illness related to Campylobacter infections and its sequelae.

2. Methodological approach

Using a stochastic simulation model we estimated the cost-of-illness and the disease burden associated with Campylobacter infections and sequelae. A previous disease burden estimate was

updated using **D**isability **A**djusted **L**ife **Y**ears (DALY's). We took into consideration each of the different health states associated with Campylobacter infection or its sequelae. For all four illnesses Dutch estimated disability weights were used (Stouthard *et al.*, 1997). The estimated annual GE incidence was based on a recent conducted population study in the Netherlands by de Wit *et al.* (2001b). GE estimates for symptom length and symptom severity were based on Dutch and English studies (Anonymous, 2000c; de Wit *et al.*, 2001a, b; van Pelt *et al.*, 2003). Annual incidence, symptom length and symptom severity GBS estimates were based on Dutch studies only (Bernsen *et al.*, 1997; van Koningsveld *et al.*, 2000). Annual incidence, symptom length and symptom severity ReA estimates were based on a recent published Finish study (Hannu *et al.*, 2002). The estimated annual incidence of Campylobacter-associated IBD cases was based on a lately conducted Danish population study (M. Helms, Serum State Institute, unpublished data). Symptom length and symptom severity IBD estimates were based on a published markov model analysis of a population-based cohort conducted in the States (Silverstein *et al.*, 1999).

Following the Dutch guidelines for human health care evaluation studies, we estimated the direct health care costs, direct non-health care costs and indirect non-health care costs associated with Campylobacter infection and its sequelae (Oostenbrink *et al.*, 2000). Dutch cost estimates for the year 2000 were used (Anonymous *et al.*, 2000a, b; Oostenbrink *et al.*, 2000). The direct health care costs considered included e.g. general practice (GP) consultations, hospitalization, drugs, rehabilitation and other medical services. Travel costs of patients and eventually co-payments by patients were considered as direct non-health care costs. Applying the friction cost method, we estimated the productivity losses (indirect non-health care costs) that occurred due to sickness leave of sick people and premature mortality, and in the case of GE, also of third persons taking care of sick persons. The friction cost method applies that production losses are only considered for the period that is needed to replace a sick, invalid or death worker, the so called friction period (Koopmanschap *et al.*, 1995, 1992).

Estimates on medical services used for the different illnesses were based, wherever available, on Dutch studies and data (Bernsen *et al.*, 2002, 2001; de Wit *et al.*, 2001b; Prismant, 2003; van Koningsveld *et al.*, 2000). In the case of ReA and IBD, we had to fall back on international published literature (Blomqvist *et al.*, 1997; Hannu *et al.*, 2002; Rösch *et al.*, 2002a, b; and others). Despite all efforts made information on the use of medical services and on the length of sickness leave of ReA patients were scarce.

The estimated DALYs and cost-of-illness with regard to the different illnesses associated with Campylobacter infections are presented both discounted and not discounted. We hereby used the officially Dutch recommended discount rate for public sector investment, which is 4 %. (Oostenbrink *et al.*, 2000). Applying a discount rate is generally used to account for the fact that e.g. health today is valued higher than health in the future, and for the fact that there is uncertainty about future possibilities to 'better' treat diseases.

3. Summarizing the main results

Within this paper only the main results are shown. Details of the assumptions made in order to estimate the incidence, the disease burden and the cost-of-illness for GE, ReA, GBS and IBD respectively, and a detailed description of the applied sensitivity analysis are available on request by the first author. We discuss in this paper only assumptions that have an important impact on our final outcomes.

3.1 Estimated incidences of Campylobacter infections and associated sequelae.

The estimated annual incidence of GE cases in the Netherlands, with a population of 16 million, was estimated to be on average 79,000 cases with a 90% confidence interval (C.I.) of 28,000 to 162,000 GE cases (table I). In nearly 30 cases is GE fatal (90% C.I.: 13-47). For some of the GE patients the Campylobacter infections resulted in sequelae, such as ReA, GBS or IBD. The annual

incidence of GE cases was by far larger than the estimated average 1400 ReA cases, the estimated average 59 GBS cases, whereof 2 fatal GBS cases and the estimated average 11 IBD cases (table I.). Therefore most cases of Campylobacter infections in humans would result only in GE. Complications such as ReA, GBS or IBD, respectively, or fatal GE and fatal GBS cases after a Campylobacter infections are relative rare. Of all sequelae related to previous Campylobacter infections, ReA is by far the most occurring sequelae.

Table I. The estimated mean, 5th, 50th and 95th percentile of annual incidences of Campylobacter-associated GE cases, ReA cases, GBS cases, IBD cases, fatal GE cases and fatal GBS cases respectively, in the Netherlands.

	Estimated annual incidence			
	5%	Mean	50%	95%
Morbidity				
C. associated GE cases	28,000	79,000	69,000	162,000
C. associated ReA cases	440	1,400	1,200	3,100
C. associated GBS cases	29	59	58	98
C. associated IBD cases	5	11	11	20
Mortality				
C. associated fatal GE cases	13	28	27	47
C. associated fatal GBS cases	0	2	2	6

3.2 Estimated disease burden due to Campylobacter infections and associated sequelae.

The estimated disease burden associated with Campylobacter infections and sequelae for the Dutch society was considerable, on average 1185 DALYs with a 90% C.I. of 693 DALYs to 1845 DALYs (table II). More than 50% of the estimated mean disease burden associated with Campylobacter infections and sequelae in the Netherlands is due to GE cases. About 25% is due to GBS cases and 11% is due to both IBD and ReA cases (figure I.). More than a third of the total estimated mean disease burden is due to YLL (figure II.). By discounting the disease burden with 4%, YLL accounts still for nearly a third of the total estimated disease burden.

Table II. Mean, 5th and 95th percentile of the estimated disease burden due to Campylobacter-associated GE cases, GBS cases, ReA cases, IBD cases and the sum of all illness cases, respectively in the Netherlands (year 2000).

Description	Disease burden					
	Not discounted			Discounted (4%)		
	5%	Mean	95%	5%	Mean	95%
Disability adjusted life years (DALYs)						
C.-associated GE	294	635	1107	239	499	873
C.-associated GBS	129	298	535	77	169	291
C.-associated ReA	40	126	279	40	126	279
C.-associated IBD	50	127	230	23	55	99
C. infections and sequelae	693	1185	1845	482	850	1377

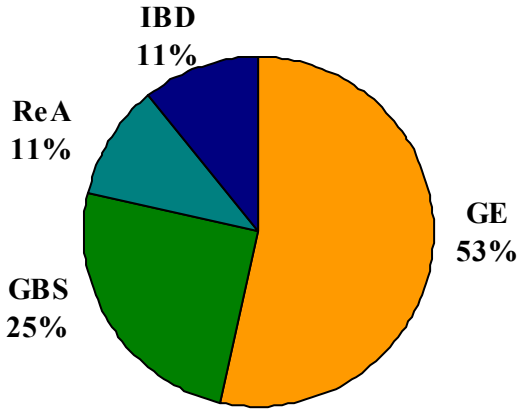

Figure I. Distribution of the estimated average annual disease burden related to Campylobacter infections and sequelae into the different illnesses for 2000 (undiscounted figures).

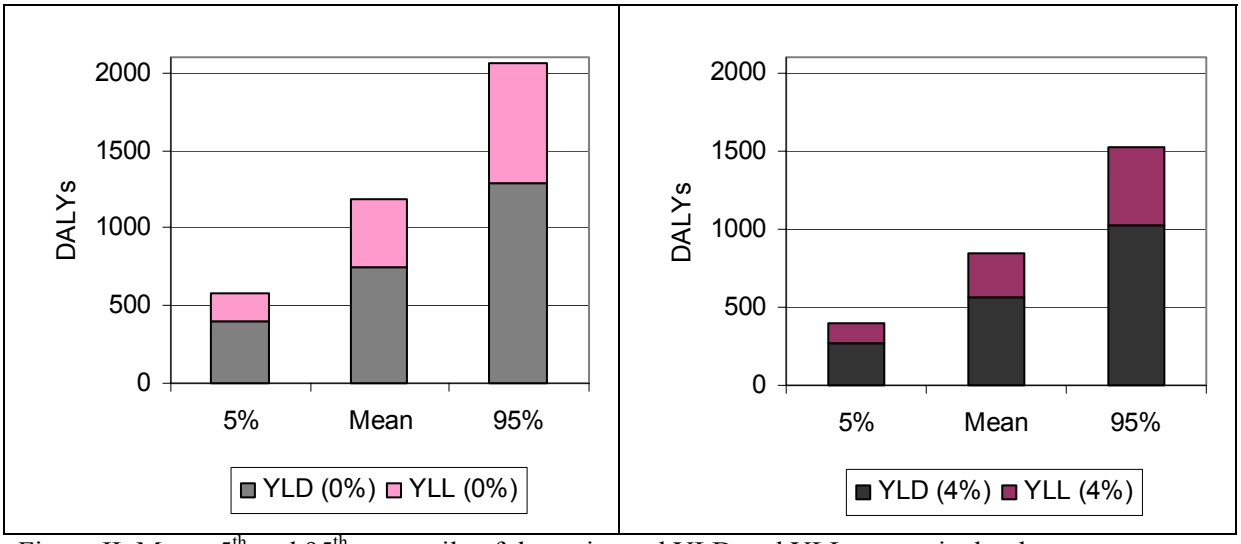

Figure II. Mean, 5th and 95th percentile of the estimated YLD and YLL respectively, due to Campylobacter-infections and sequelae in the Netherlands (year 2000).

By dividing the average estimated DALYs by the average estimated annual incidence, we obtain an estimate of the 'average' DALYs/case. Chronic and long-lasting diseases, such as IBD and GBS, are responsible for higher disease burden per patient than short disease episodes, such as gastro-enteritis. To provide with insight into the relative disease burden of all Campylobacter-associated diseases, we have summarized the estimated DALYs/1000 average cases for all four Campylobacter-associated illnesses and the estimated DALYs associated with Campylobacter infections and sequelae per initial GE cases. Results are summarized in table III.

Table III. Mean estimate of DALYs/1000 cases for average GE cases, GBS cases, ReA cases and IBD cases, respectively, all associated with Campylobacter infections (year 2000).

	Not discounted DALYs/ 1000 average cases
DALYs due to GE/C. associated GE cases	8
DALYs due to GBS/ C. associated GBS cases	5,000
DALYs due to ReA/ C. associated ReA cases	90
DALYs due to IBD/ C. associated IBD cases	11,600
DALYs due to C.-infections and sequelae/C. associated GE cases	15

3.3 Estimated cost-of-illness due to Campylobacter infections and associated sequelae.

The estimated cost-of-illness associated with Campylobacter infections and sequelae in the Netherlands for the year 2000 were with on average more than 20 million € (range 10 – 38 million € 90 C.I.) considerable (table IV). Indirect non-health care costs accounted for nearly 2/3 of the estimated average total cost-of-illness, whereas direct health care costs accounted for approximately 1/3. Direct non-health care costs were only of minor importance (table IV).

Indirect non-health care costs, which were mainly productivity losses, accounted for approximately 90% of the total cost-of-illness related to GE cases. Whereas direct health care costs accounted for approximately 70% of the estimated cost-of-illness associated with IBD and GBS cases, respectively. The direct non-health care costs were only minor (less than 1% of total costs). The indirect non-health care costs related to GE cases is by far the greatest cost category in our estimated total cost-of-illness (figure III). Therefore it is not surprising that indirect non-health care costs accounted for approximately 2/3 of the estimated average total cost-of-illness.

Table IV. Mean, 5th, 50th and 95th Percentile of the estimated direct health care costs, direct non-health care costs, indirect non-health care costs and total costs respectively, all related to Campylobacter infections and sequelae for 2000 (undiscounted figures).

Description	Estimated costs (*1000 €) for the year 2000			
	5%	Mean	50%	95%
Direct health care costs	4,000	6,500	6,400	9,800
Direct non-health care costs	16	51	49	122
Indirect non-health care costs	5,200	14,000	12,600	29,400
Total costs	10,000	20,600	19,000	38,000

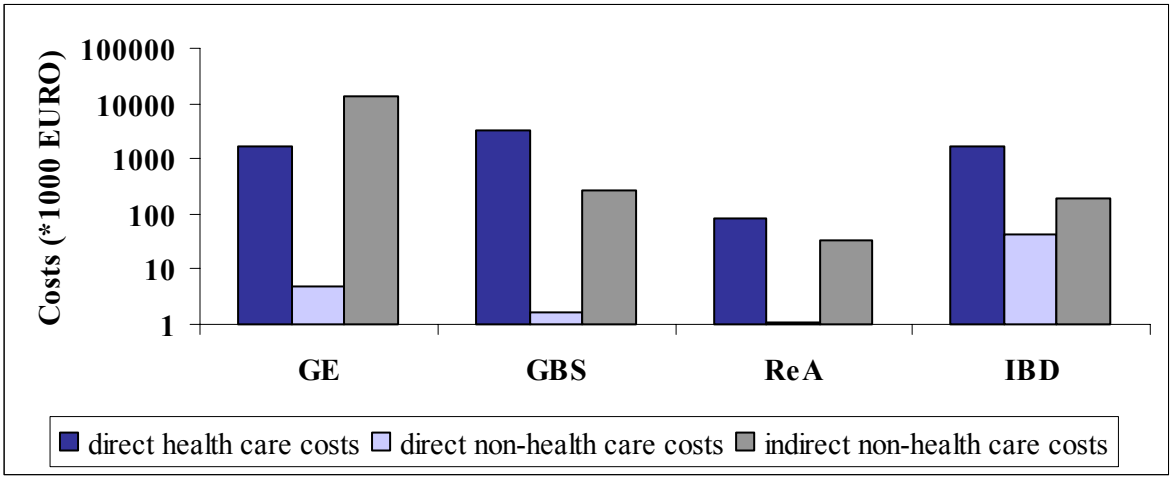

Figure III. The mean estimated direct health care costs, direct non-health care costs and indirect non-health care costs due to Campylobacter-associated GE cases, GBS cases, ReA cases and IBD cases respectively, for 2000 (undiscounted figures).

For GE and ReA all costs were assumed to occur within the first year. In the case of GBS most costs would occur in the first years after disease onset and only for IBD, the associated cost-of-illness were assumed to be equally spread over the remaining life years of the patients after disease onset. Given that IBD cases accounts for ~10% of the total costs, discounting has, as shown in table V, only little impact on the estimated cost-of-illness related to Campylobacter infections and sequelae.

Under the current assumptions, approximately 2/3 of the estimated mean cost-of-illness related to Campylobacter infections and sequelae in the Netherlands are made by GE cases, see figure IV. Of the estimated mean cost-of-illness about 17% were estimated to be made by GBS cases and 9% were

estimated to be made by IBD cases. ReA cases accounted for only 1% of the estimated mean cost-of-illness. However, in the current study the cost-of-illness related to ReA cases were probably underestimated.

Table V. Mean, 5th and 95th percentile of the estimated cost-of-illness associated with Campylobacter infection and sequelae in the Netherlands, total and for each illness (year 2000).

Description	Estimated cost-of-illness (*10^6 €) for the year 2000					
	Not discounted			Discounted (4%)		
	5%	Mean	95%	5%	Mean	95%
C. associated-GE	6.1	15.1	30.9	6.1	15.1	30.9
C. associated-GBS	1.3	3.4	6.4	1.3	3.3	6.3
C. associated-ReA	0.0[1]	0.0[1]	0.1	0.0[1]	0.0[1]	0.1
C. associated-IBD	0.7	1.9	3.4	0.3	0.9	1.5
Total costs	10.0	20.6	38.0	9.2	19.4	36.4

[1)] Less than 0.1 million €.

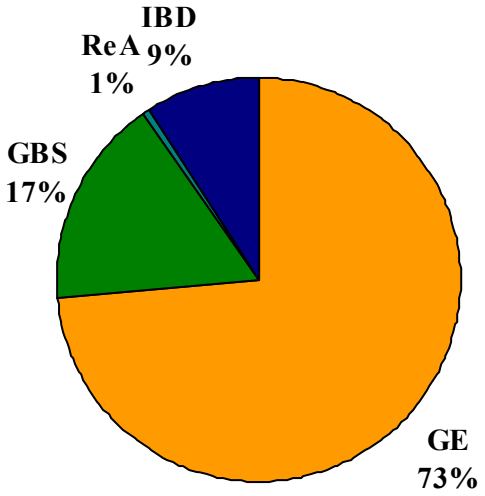

Figure IV. Distribution of the estimated total cost-of-illness due to Campylobacter infections and sequelae into the different illnesses for the year 2000 (undiscounted figures).

We further have summarized in table VI the estimated mean cost-of-illness per estimated GE case, GBS case, ReA case and IBD case, respectively, for the year 2000. For GE cases, we have considered the average costs due to GE only/GE case and the average costs due to GE and sequelae/GE case. The estimated costs per estimated ReA cases might be underestimated, as mentioned already earlier. Especially chronic and long-lasting diseases such as GBS and IBD resulted in high cost-of-illness per estimated case, opposite to e.g. the relative short GE episode/ average case.

Table VI. Average estimate of cost-of-illness/ cases for an average Campylobacter-associated GE case, GBS case, ReA case and IBD case, respectively in the Netherlands for 2000 (undiscounted figures).

	Average cost-of-illness (€)/average case
Costs due to GE/C.-associated GE case	190
Costs due to GBS/C.-associated GBS case	58,000
Costs due to ReA/C.-associated ReA case	20
Costs due to IBD/C.-associated IBD case	173,000
Costs due to GE & sequelae/C.-associated GE case	260

3.4 Sensitivity analysis

Due to model uncertainties and the non-availability of some data, assumptions had to be made. With the help of sensitivity analyses the impact of such assumptions was analyzed. Details of the different assumptions and their impact on the results are available on request from the first author. In the following paragraph we only summarize those assumptions that had an important effect on our results.

- The assumed length of symptoms and the assumed sickness leave of GE cases *not* visiting a GP (approximately 2/3 of all GE cases) had a major impact on the assumed cost-of-illness. For example half a day longer (shorter) sickness leave/patient resulted in an increase (decrease) of the estimated total costs by more than 1 million €. Whereas the impact on the estimated disease burden was relative small.
- Given the large uncertainty of the population at risk to develop ReA after a Campylobacter infection, the assumed annual incidence of ReA cases had a major impact on the estimated disease burden. Assuming that on average 1400, 400 and 5,800 cases would develop ReA, resulted in an average estimated disease burden of 126, 38 and 520 DALYs respectively.
- More detailed knowledge about medicine use and sickness leave for ReA patients would probably result in a higher estimate of the cost-of-illness. But the total estimated costs due to ReA would probably remain to be the lowest costs of all sequelae associated with Campylobacter infections.

4. Discussion

The annual incidences of Campylobacter-associated GE cases, ReA cases, GBS cases and IBD cases in the Netherlands, with a population of 16 million, was estimated to be on average ~ 79,000, 1400, 59 and 11 cases respectively. Most cases of Campylobacter infections in humans would result only in GE. Complications such as ReA, GBS or IBD, respectively, or fatal cases after a Campylobacter infections are relative rare. Of all sequelae related to previous Campylobacter infections, ReA is by far the most occurring sequelae, but in most cases also by far the less sever sequelae. Even if we would assume that only positive laboratory-confirmed Campylobacter infections could result in ReA, ReA would stay by far the most occurring sequelae after a previous Campylobacter infection.

The estimated disease burden associated with Campylobacter infections and sequelae was with on average nearly 1200 DALYs slightly lower than the estimate of the previous Dutch disease burden study, which was on average 1400 DALYs. The estimated number of fatal GE cases and the estimated YLL are in both studies comparable. Disease burden due to non-fatal GE cases, ReA and GBS were in our study always slightly lower than in the earlier study. In the case of non-fatal GE cases, the difference was mainly due to the lower annual incidence assumed in our study. Consequently the annual ReA incidence was assumed to be lower as well. Although, we assumed the same annual GBS incidence, our estimate was slightly lower due to slightly elderly GBS patients. We used in our study another more representative dataset that included more patients from a larger geographic area.

The greatest part of the estimated disease burden related to Campylobacter infections and sequelae was due to GE cases. But fatal GE cases, on average 30 cases, accounted for more than 1/3 of the total estimated disease burden related to GE cases. Further it has to be notified that patients with chronic and long-lasting illnesses, such as IBD and GBS, had a larger impact on the estimated disease burden than the large amount of non-fatal GE cases.

The population at risk for developing ReA after a Campylobacter infection needs to be better defined in future research. Assuming that: a) all Campylobacter-associated GE cases visiting a GP (BASE) develop ReA; b) only positive laboratory-confirmed Campylobacter cases develop ReA; or c) all Campylobacter-associated GE cases might develop ReA, large differences in the estimated annual incidence of ReA cases were found. Consequently, also the estimated disease burden related to ReA varied a lot. With a better estimate of the 'real' number of ReA cases, it might be expected that also

the estimated cost-of-illness varies enormously. Future research is needed in order to get a more reliable estimate of the population at risk.

By applying the friction cost method, the estimated indirect non-health care costs related to chronic and/or long-lasting illnesses, and related to fatal cases, are by far lower than found in other studies. Former studies have used the human capital method, which is known for resulting in far higher estimates of productivity losses (*potentially* lost income as a consequence of disease considered). Apart from the considerable disease burden estimate, the estimated cost-of-illness associated with Campylobacter infections and sequelae were with on average more than 20 million € (range 10 – 38 million € 90 C.I.) also of importance. Therefore, when comparing our estimates with cost-of-illness estimates of other studies, differences in study methodology should be taken into account.

Of the average estimated 20 million € total cost-of-illness, was the greatest part due to GE cases. Hereby played the productivity losses due to sickness leave of GE cases an important role. However, when comparing the estimated average costs per average case per illness, average IBD and average GBS patients were by far costlier to the Dutch society than for example GE patients.

Given that productivity losses due to sickness leave of GE cases was one of the major costs of the total cost-of-illness related to Campylobacter infections and sequelae, better estimates of the length of sickness leave of especially GE patients not visiting a GP might help to improve the estimate. In case of for example half a day shorter sickness leave the estimate will have to be corrected downwards by more than 1 million €, whereas a longer sickness leave (+0.5 days) will raise the estimate of the cost-of-illness by more than 1 million €. Furthermore, newly available data, especially on ReA but also on additional aids and tools for GBS cases might help to improve the estimate of the cost-of-illness related to Campylobacter infections and sequelae. The latter cost component, however, will probably result in a higher estimate of the cost-of-illness than our estimate. Therefore, we regard the current estimate of the cost-of-illness related to Campylobacter infections and sequelae as an underestimation rather than an overestimation of the real costs.

Despite all the shortcomings of this study, we could update the previous estimate on the disease burden related to Campylobacter infections and sequelae, whereby using new available data and knowledge. Further, this study is the first estimate of a cost-of-illness for the Dutch society considering not only Campylobacter-associated GE cases, but also associated sequelae. No earlier estimates of the cost-of-illness for the Dutch society associated with ReA, GBS and IBD were available. And although we considered in this study only the costs related to Campylobacter-associated ReA, GBS and IBD cases, our results are a first step into estimating the cost-of-illness of ReA, GBS and IBD.

5. Outlook

The complex epidemiology of Campylobacter infections and sequelae and the limited available knowledge requires a well-balanced set of measure in order to prevent Campylobacter infections in humans effectively. With the goal to advise the Dutch government on the effectiveness and efficiency of measures aimed at reducing Campylobacter infections and sequelae in the Dutch population, the so-called CARMA (**Campylobacter R**isk **M**anagement and **A**ssessment) project was launched. These CARMA project is mainly characterized by two key questions:

1) What are the most important routes by which the Dutch population is exposed to Campylobacter and can the contribution of these routes is quantified?
2) Which (sets of) measures can be taken to reduce the exposure to Campylobacter, what is their expected efficiency and societal support?

For the Netherlands chicken meat was defined to be the major route of human Campylobacter infections, - approximately 40% of all human Campylobacter infections cases. Therefore within the CARMA project it was decided to focus in first instance on the chicken meat production chain. Next to a risk assessment an economic evaluation is needed in order to answer the second key question. Within the CARMA project an economic evaluation of different interventions in the chicken meat chain to reduce human Campylobacter infections will take place in the form of a cost-effectiveness analysis. The costs of the intervention applied in the chicken meat chain will be related to ‘reduced’

burden of disease and 'reduced' costs of illness. This will result in a cost-effectiveness ratio that should express the relative efficiency of several policy options to reduce the number of Campylobacter infections. As a first step in such an economic evaluation, the disease burden estimate and the cost-of-illness estimate associated with Campylobacter infections and sequelae is described in this paper.

6. References

Anonymous (2000a). *Farmacotherapeutisch kompas 2000/2001*. Amstelveen, The Netherlands: College Tarieven Gezondheidszorg.

Anonymous (2000b). *Tariefboek medisch specialisten - jaar 2000*. Amstelveen, The Netherlands: College Tarieven Gezondheidszorg.

Anonymous (2000c). *A report of the study of infectious intestinal disease in England*. London, UK: The Stationery Office.

Bernsen, R.A., Jacobs, H.M., de Jager, A.E. and van der Meché, F.G.A. (1997). Residual health status after Guillain-Barré syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry* 62: 637-640.

Bernsen, R.A., Jager, A.E., Schmitz, P.I. and van der Meche, F.G.A. (2001) Long-term sensory deficit after Guillain-Barre syndrome. *Journal of Neurology* 248 (6): 483-486.

Bernsen, R.A., de Jager, A.E., Schmitz, P.I. and van der Meche, F.G.A. (2002) Long-term impact on work and private life after Guillain-Barre syndrome. *Journal of Neurological Sciences* 201 (1-2): 13-17.

Blomqvist, P. and Ekbom, A. (1997). Inflammatory bowel diseases: health care and costs in Sweden in 1994. *Scandinavian journal of gastroenterology* 32 (11): 1134-1139 .

De Wit, M.A., Koopmans, M.P., Kortbeek, L.M., van Leeuwen, N.J., Bartelds, A.I. and van Duynhoven, Y.T. (2001a). Gastroenteritis in sentinel general practices,The Netherlands. *Emerging infectious diseases* 7 (1): 82-91.

De Wit, M.A.S., Koopmans, M.P.G., Kortbeek, L.M., Wannet, W.J.B., Vinje, J., Van Leusden, F., Bartelds, A.I.M. and van Duynhoven Y.T. (2001b). Sensor, a population-based cohort study on gastroenteritis in the Netherlands: incidence and etiology. *American journal of epidemiology* 154 (7): 666-674.

Hannu, T., Mattila, L., Rautelin, H., Pelkonen, P., Lahdenne, P., Siitonen, A. and Leirisalo-Repo, M. (2002). Campylobacter-triggered reactive arthritis: a population-based study. *Rheumatology* 41(3): 312-318.

Havelaar, A.H., de Wit, M.A.S. and van Koningsveld, R. (2000a). *Health burden in the Netherlands (1990-1995) due to infection with thermophilic Campylobacter species*. RIVM report no. 284550 004.Bilthoven, the Netherlands: Rijksinstituut voor volksgezondheid en milieu.

Havelaar, A.H., de Wit, M.A.S., van Koningsveld, R. and van Kempen, E. (2000b). Health burden in the Netherlands due to infection with thermophilic Campylobacter spp. *Epidemiology and Infection* 125 (3): 505-522.

Koopmanschap, M.A., Rutten, F.F., van Ineveld, B.M. and van Roijen, L. (1995). The friction cost method for measuring indirect non-health care costs of disease. *Journal of Health Economics* 14 (2): 171-189.

Koopmanschap, M.A. and van Ineveld, B.M. (1992). Towards a new approach for estimating indirect non-health care costs of disease. *Social Science and Medicine* 34 (9): 1005-1010.

Oostenbrink, J.B., Koopmanschap, M.A. and Rutten, F.F.H. (2000). *Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg*. Amstelveen, the Netherlands: College voor zorgverzekeringen.

Prismant (2003). Ziektenhuisstatistieken - Landelijk gemiddelde verpleegduur per diagnose. Utrecht, the Netherlands: Prismant. http://www.prismant.

Rösch, M., Leidl, R., Thomas, S., von Tirpitz, C., Reinshagen, M., Adler, G. and Konig, H.H. (2002a) Messung der ambulanten Behandlungskosten von chronisch entzündlichen Darmerkrankungen an einer deutschen Universitätsklinik. *Medizinische Klinik* 97 (3): 128-136.

Rösch, M., Leidl, R., Tirpitz, C., Reinshagen, M., Adler, G. and Konig, H.H. (2002b). Kostenerfassung bei chronisch-entzündlichen Darmerkrankungen durch direkte Patientenbefragung mit einem Kostenwochenbuch. *Zeischrift für Gastroenterologie* 40 (4): 217-228.

Silverstein, M.D., Loftus, E.V., Sandborn, W.J., Tremaine, W.J., Feagan, B.G., Nietert, P.J., Harmsen, W.S. and Zinsmeister, A.R. (1999). Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology* 117 (1): 49-57 .
Stouthard, M.E.A., Essink-Bot, M.-L., Bonsel, G.J., Barendregt, J.J., Kramers, P.G.N., van de Water, H.P.A., Gunning-Schepers, L.J. and van der Maas, P.J. (1997). *Disability weights for diseases in the Netherlands*. Rotterdam, the Netherlands: Departement of Public Health, Erasmus University Rotterdam.
Van Koningsveld, R., van Doorn, P.A., Schmitz, P.I.M., Ang, C.W. and van der Meché, F.G.A. (2000). Mild forms of Guillain-Barré syndrome in an epidemiological survey in the Netherlands. *Neurology* 54: 620-625.
Van Pelt, W., de Wit, M.A.S., Wannet, W.J.B., Ligtvoet, E.J.J., Widdowson, M.A. and van Duynhoven, Y.T.H.P. (2003). Laboratory surveillance of bacterial gastroenteric pathogens in the Netherlands, 1991-2001. *Epidemiology and Infection* 130 (2): 1-11.