CellPress REVIEWS

Science & Society

Foodborne Parasitic Diseases in Europe: Social Cost-Benefit Analyses of Interventions

Lucy J. Robertson,[1,*] Paul R. Torgerson,[2] and Joke van der Giessen[3]

Social cost-benefit analysis (SCBA) can be used to evaluate the benefit to society as a whole of a particular intervention. Describing preliminary steps of an SCBA for two foodborne parasitic diseases, echinococcosis and cryptosporidiosis, indicates where data are needed in order to identify those interventions of greatest benefit.

What Are SCBAs?

Every morning I leave my office for about 30 min, walk to the canteen, and buy a cup of coffee. If I buy a packet of coffee and make the coffee in my office, in how many days will I save money after my official outlay? To analyze this seriously, I need to include not just the cost of the coffee, but also the coffee maker, the electricity, the cup, the washing-up liquid, etc. Cost-benefit analyses of this personal type are conducted daily by individuals in order to determine whether the expense of any activity will be covered by the benefit derived from that activity; such analyses frequently contain a time element and are often viewed from a single perspective. In this example, the effect of the proposed action on the canteen was not considered. Furthermore, this analysis does not include the less tangible costs and benefits, such as the social benefit from interactions in the canteen, the positive health effects of the walk, the time expended, the long-term effects on wellbeing, etc.

If the intention is to include all possible variables, including those on which placing a price is not obvious, and reach a decision on what is best for society, rather than an individual entity, an SCBA is conducted. Thus, the intention of an SCBA is to evaluate an action from the perspective of society as a whole. Such SCBAs are often conducted for appraisal of publicly financed investment projects, so that available resources are allocated in the manner that is of most benefit to society [1]. SCBAs have been widely used in evaluating implementation of drinking water interventions, where they not only enable aggregation of indicators into a single number index by weighting, including productivity gains, time saving, and health benefits, but also because they enable incorporation of time to achievement of sustainability [2]; more recently, an SCBA for preventive interventions for toxoplasmosis has been designed in The Netherlands [3].

Why SCBAs for Foodborne Parasitic Diseases?

One reason that foodborne parasites (FBPs) are neglected pathogens is that they often result in chronic diseases and sequelae, and have long incubation times (e.g., acquired toxoplasmosis and development of blindness after 20 years). Many of these diseases (such as neurocysticercosis) are most prevalent in disadvantaged societies. Several FBP diseases are associated with nonspecific symptoms and the effects may not be overt; thus, they are often associated with relatively few disability-adjusted life years (DALYs) at the individual level due to the known difficulty in quantifying such outcomes, along with the lack of obvious association with some sequelae [4]. Thus, their impacts on public society due to consequences for both cognitive and physical development, as well as economic productivity and general wellbeing, may be masked [5]. Various approaches have been applied for ranking diseases according to their relevance and impact, and have also been applied to diseases caused by FBPs [6]. Although many such ranking approaches focus predominantly on morbidity/mortality and disease-burden estimates (DALYs), some methods also attempt to include other criteria, such as the socioeconomic impact [6]. After identifying the highest ranked FBP, intervention strategies to reduce the disease burden can be assessed. For evaluation of different intervention strategies, and determining the most appropriate, use of an SCBA is of particular relevance.

Although an unusual parasite in Europe, *Taenia solium* is presently considered the most important FBP globally, based largely on DALYs due to cysticercosis [7], and interventions for control have often been considered loosely from an SCBA perspective. The 'basket of options' approach describes potential interventions for *T. solium*, but does not consider their effects in detail in terms of an SCBA [8]. In The Netherlands, among 14 foodborne diseases evaluated, toxoplasmosis had one of the highest disease burdens, and prompted the design of a stepwise approach to an SCBA for preventive measures [3]; this has been the starting point of the preliminary stage described here.

The complexity of many FBPs, often with zoonotic reservoirs or multiple hosts in their life cycles, means that using the SCBA approach may provide an optimal overview for assessing the value of different interventions. Key terms and concepts that are involved in an SCBA for FBPs are outlined in Box 1.

What Data Do We Need to Apply an SCBA to Foodborne Parasites?

Performing an SCBA implies identification and valuation of all the effects of a certain intervention. SCBAs are rarely performed

Box 1. Glossary of Relevant Terms and Concepts for an SCBA

Key concepts and terms	Definition or explanation
Animal life equivalent (ALE)	A time trade-off equivalent of animal disease losses in terms of healthy years of human life lost
Cost-effectiveness threshold	A threshold set so that the interventions that appear to be relatively good or very good value for money can be identified. For example, interventions that avert one DALY for less than average per capita income for a given country or region are considered very cost-effective
Disability-adjusted life year (DALY)	DALY is the sum of years lived in disability and years of life lost
Healthy life lost due to disability (YLD)	Equivalent years of life lost due to disability as a result of a nonfatal disease. This is estimated from the disability weight caused by disease or injury which is on a scale of 0 to 1 multiplied by the duration of the disease or injury.
Minimum DALY value	A minimum or threshold monetary value for the DALY which is independent of the local wealth or GDP per head. This sets a global baseline for cost effectiveness
Social cost-benefit analysis (SCBA)	A systematic and cohesive method to survey all the impacts caused by a disease prevention intervention or other policy measure.
Value of a life year lost (VOLY)	The monetary values of a year of life lost.
Value of statistical life (VOSL)	An estimate for how much people are willing to pay to reduce their risk of death.
Willingness to pay	The maximum amount an individual is willing to pay to avoid illness, injury or death.
Years of life lost (YLL)	Number of years of life lost due to premature mortality. Calculated as the residual life expectancy at the time of death.
zDALY	A composite measure to estimate the burden of zoonotic diseases that have an impact on both humans and animals. It consists of the DALY + ALE

when evaluating interventions affecting both human and animal health. Evaluations usually focus either on animal health or on public health domains, each ignoring the other sector. For diseases caused by FBPs, control strategies should take into account expected changes in both human and animal domains, where animal health losses and interventions in the animal reservoirs implicate costs – and potentially benefits – but an overall consequence of the interventions will be a reduced disease burden, resulting in benefits for the human population. Monetary units are used in calculating an SCBA such that every item is first accounted for in the logical units associated with that factor, and then converted to a monetary unit. If an activity being evaluated has an effect on human morbidity or mortality, then the value associated with averted DALYs raises the question of their value, and whether this should vary according to geographical location [9]. To overcome this, human burden could be converted to monetary losses, and various methods have been suggested that give DALYs a monetary value, usually through the use of local per capita gross domestic product (GDP) or gross national income (GNI) [9–11]. Cost-effectiveness thresholds (often used to define when health interventions are worthwhile) tend to reflect national budgets and willingness to pay; but such values are not appropriate for international comparisons, and it has been argued that a minimum DALY value is the logical solution [12]. Alternatively, animal health losses could be converted to an animal life equivalent (ALE) value, and this sum could be added to the DALY, resulting in the overall societal burden that incorporates both animal health and human health, in terms of a zDALY [13].

Preliminary Steps in Considering SCBAs for Some Foodborne Parasites in Europe

A recent workshop held as part of COST Action Euro-FBP (see Acknowledgments) provided the opportunity to take preliminary steps for considering SCBAs for relevant FBPs in Europe. During the workshop, those parasites that had been ranked as being the top-five in importance in Europe [14] were considered: *Echinococcus multilocularis*, *Toxoplasma gondii, Trichinella spiralis, Echinococcus granulosus,* and *Cryptosporidium* spp. Due to the work already completed for *T. gondii* [3], this FBP was not assessed further during the workshop.

Given the importance globally, as well as regionally, of cystic and alveolar echinococcosis and cryptosporidiosis, initial steps for an SCBA for both of these parasitic diseases are used as illustrations of this approach.

Cryptosporidiosis: *Cryptosporidium* spp. Scoping the Problem

Cryptosporidiosis in humans is caused by infection by various species of *Cryptosporidum*, with *C. hominis* and *C. parvum* responsible for most infections. This parasite occurs globally, and the human burden of cryptosporidiosis has been estimated at 2.16 million DALYs per annum [6]. Several species of *Cryptosporidium* are zoonotic, but of particular importance for human infection is

Table 1. Domains and Stakeholders Related to the Interventions for Reducing Transmission of (A) Cryptosporidiosis and (B) Alveolar and Cystic Echinococcosis through Contaminated Fresh Produce

Reducing transmission of cryptosporidiosis			Reducing transmission of alveolar and cystic echinococcosis		
Intervention	Domain/stakeholders	Potential benefits of intervention	Intervention	Domain/stakeholders	Potential benefits of intervention
Educational (compulsory training for farm managers, veterinarians etc.; public information; social media)	Crop producers (farmers and farm employees); Consumers; Government (health insurance costs); Public/society (health, wellbeing and productivity)	Knowledge on transmission routes resulting in reduction in contamination, thus reduction in transmission and infection, and reduced societal costs or wastage (education, productivity losses, pensions)	Educational (compulsory training for dog owners, hunters, veterinarians, farmers, diagnosticians etc.; public information; social media)	Crop producers (farmers and farm employees); Dog owners and hunters; Gatherers of wild food (berries, mushrooms); Veterinarians; Consumers; Diagnosticians/doctors; Government (health insurance costs); Public/society (health, wellbeing and productivity)	Knowledge on transmission routes resulting in reduction in contamination, thus reduction in exposure, transmission (to normal and aberrant (human) intermediate hosts) and infection, earlier diagnosis, and reduced societal costs or wastage (education, productivity losses, pensions)
Improved management practices (e.g., separation of animals and food crops, use and storage of manure, selection of irrigation water sources, hygiene interventions)	Crop producers (farmers and farm employees); Consumers; Government (health insurance costs); Public/society (health, wellbeing and productivity)	Reduction in initial contamination due to specific reduction in contact between crops and oocysts, thus reduction in transmission and infection, and reduced societal costs or wastage (education, productivity losses, pensions)	Treatment and management of definitive canid hosts: Dogs (*E. granulosus*, *E. multilocularis*): exposed dogs treated at predefined intervals; prevention of ingestion of infected intermediate hosts (CE: offal, slaughter waste; AE: infected rodents) Foxes (*E. multilocularis*): continuous distribution of bait containing antihelmintic in predefined areas; restriction of fox intrusion into urban areas by garbage management	Farmers and farm employees; Veterinarians; Dog owners; Hunters; Landowners; Officials, local government; Consumers; Government (health insurance costs); Public/society (health, wellbeing and productivity)	Reduction in prevalence in dogs (*E. granulosus, E. multilocularis*) and foxes (*E. multilocularis*); reduction in potential for contamination, and thus reduction in exposure and transmission (to normal and aberrant (human) intermediate hosts) and infection, and reduced societal costs or wastage (education, productivity losses, pensions)
Post-harvest interventions (e.g., high-pressure processing, gamma irradiation)	Post-harvest domains (depots, handlers, sales); Consumers; Government (health insurance costs); Public/society (health, wellbeing and productivity)	Inactivation of oocysts on fresh produce, thus reduction in transmission and infection, and reduced societal costs or wastage (education, productivity losses, pensions)	Management and treatment of intermediate hosts: appropriate slaughter-waste management (CE); culling of elderly sheep; vaccination of livestock (particularly sheep) in appropriate areas	Farmers; Veterinarians; Slaughterhouses; Legislators and government; Pharmaceutical companies; Consumers; Government (health insurance costs); Public/society (health, wellbeing and productivity)	Decreased prevalence in livestock (intermediate hosts for CE), reduced transmission to dogs, and thus reduced prevalence in dogs – with long-term result of reduction in exposure and transmission (to normal and aberrant (human) intermediate hosts) and infection, and reduced societal costs or wastage (education, productivity losses, pensions)

C. parvum, which commonly infects young ruminants, resulting in an additional animal health burden. Most relevant transmission routes (to humans) are direct faecal–oral (animal–human, human–human), via water (drinking, recreational, irrigation, wash), and via food (fresh produce, juice, dairy). As transmission via fresh produce appears to be an emerging threat, interventions targeted towards this route should be of interest.

Three potential groups of interventions can be identified, and these, along with the domains and effects resulting in costs and benefits established for these are described in the Table 1, based on the SCBA model for toxoplasmosis [3].

Cystic and Alveolar Echinococcosis: *E. granulosus* and *E. multilocularis* Scoping the Problem

Cystic echinococcosis (CE) is caused by larval stages of *E. granulosus sensu lato* and results in 188 000 new cases and a burden of 184 000 DALYs per annum globally. The more malignant alveolar echinococcosis (AE) caused by *E. multilocularis* results in 18 500 new cases per annum, but results in 688 000 DALYs annually [6], the higher burden reflecting the high case fatality rate if untreated. In these diseases, humans (aberrant intermediate hosts) become infected by ingestion of eggs shed by the canid definitive hosts. Ingestion of eggs may occur either by direct contact with infected dogs or foxes, or through environmental contamination and subsequent spread to food, resulting in foodborne transmission. Symptoms of clinical disease occur after a prolonged incubation period due to development of cysts (CE) or proliferative metacestode vesicles (AE) in internal organs, particularly liver and lungs. In Europe, the population fraction of human echinococcosis, both cystic and alveolar, attributable to contaminated food is likely to be considerable, although precise figures derived from empirical data are unavailable. Expert elicitation indicates wide uncertainty for both CE (4–40% of cases) and AE (12–79% of cases) [15], and discussions on risk factors based on systematic review and meta-analysis (e.g., [16]) indicate the need for more primary studies. However, these can be a challenge due to the long latent period between infection and appearance of clinical signs.

Three potential interventions, in rural endemic areas, for both diseases are identified, and these, along with the domains and effects resulting in costs and benefits established for the interventions, as previously described for cryptosporidiosis, are included in Table 1.

Conclusion: Are SCBAs Feasible or Appropriate for Important FBPs in Europe?

SCBAs depend on the availability of high-quality data. For all three parasites considered here, the actual incidence of human cases is probably underestimated, and empirical data on the food-attributable proportion of cases are lacking. Nevertheless, for cryptosporidiosis, a relatively acute disease and for which foodborne outbreaks have been identified and documented, a preliminary SCBA seems possible, although this would be improved with better data. DALYs are an important input, and therefore improved human surveillance in European countries is needed. Although both CE and AE are chronic diseases, and prevalence data are probably underestimated, in areas of high endemicity it should be feasible to conduct an SCBA for CE. Improved human and slaughterhouse surveillance would improve the available data (e.g., the European Register of Cystic Echinococcosis; [17]). For AE in Europe, for which the associated parasite life cycle is largely in wildlife, data are currently insufficient for an SCBA. However, based on the potential for spread of this parasite, improved human surveillance could provide useful data for a future SCBA.

Acknowledgments

This work was a collaboration within the framework of Euro-FBP, the European Network for Foodborne Parasites, COST Action FA1408.

We acknowledge the contributions of the following participants at the SCBA workshop held at RIVM, Bilthoven, The Netherlands, during January 2018.

Participants at the workshop were: Ewa Bilska-Zajac (Państwowy Instytut Weterynaryjny, Poland), Ilias Chaligiannis (Veterinary Center of Thessaloniki, Greece), Jenny Deng (RIVM, The Netherlands), Ardine de Wit (RIVM, The Netherlands), Jacinto Gomes (Instituto Nacional de Investigação Agrária e Veterinária, Portugal), Lisa Guardone (University of Pisa, Italy), Istvan Kucsera (National Public Health Institute, Hungary), Marie Jose Mangen (RIVM, The Netherlands), Axel Marinovic (RIVM, The Netherlands), Anne Mayer-Scholl (BFR, Germany), Marieke Opsteegh (RIVM, The Netherlands), Elias Papadopoulos (Aristotle University of Thessaloniki, Greece), Jelena Petrovic (Novi Sad, Serbia), Katharina Riehn (HAW-Hamburg, Germany), Gereon Schares (Friedrich Loeffler Institute, Germany), Smaragda Sotiraki (Veterinary Research Institute, Greece), Jacek Sroka (Państwowy Instytut Weterynaryjny, Poland), Anita Suijkerbuijk (RIVM, The Netherlands), Mario Sviben (Croatian National Institute of Public Health, Croatia), Adriana Titilinca (University of Agricultural Science and Veterinary Medicine, Romania), Isabelle Vallee (ANSES, France), Paul van Gils (RIVM, The Netherlands), Sasa Vasilev (INEP, Serbia), Helga Waap (Instituto Nacional de Investigação Agrária e Veterinária, Portugal).

[1]Parasitology Laboratory, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, PO Box 369 Sentrum, 0102 Oslo, Norway
[2]Section of Epidemiology, Vetsuisse Faculty, University of Zürich, Winterthurerstrasse 270, 8057 Zürich, Switzerland
[3]Centre for Zoonoses and Environmental Microbiology, National institute for Public Health and the Environment (RIVM), PO Box 9, 3520 BA Bilthoven, The Netherlands

*Correspondence:
lucy.robertson@nmbu.no (L.J. Robertson).
https://doi.org/10.1016/j.pt.2018.05.007

References

1. Thirlwall, A.P. (1994) Project appraisal, social cost-benefit analysis and shadow wages. In *Growth and Development* (Thirlwall, A.P., ed.), pp. 195–210, Palgrave
2. World Health Organization (2011) *Valuing Water, Valuing Livelihoods: Guidance on Social Cost-Benefit Analysis of Drinking-Water Interventions, with Special Reference to Small Community Water Supplies*, 262 pp., IWA Publishing
3. Suijkerbuijk, A.W.M. *et al.* (2018) The design of a social cost-benefit analysis of preventive interventions for

toxoplasmosis: an example of the One Health approach. *Zoonoses Pub. Health* 65, 185–194

4. World Health Organization, Department of Information, Evidence and Research Geneva (2017) *WHO Methods and Data Sources for Global Burden of Disease Estimates 2000–2015. Global Health Estimates Technical Paper WHO/HIS/IER/GHE/2017.1.* Available at: http://www.who.int/healthinfo/global_burden_disease/GlobalDALYmethods_2000_2015.pdf?ua=1
5. Steinmann, P. *et al.* (2010) Multiparasitism a neglected reality on global, regional and local scale. *Adv. Parasitol.* 73, 21–50
6. Devleesschauwer, B. *et al.* (2017) Risk ranking of food-borne parasites: state of the art. *Food Waterborne Parasitol.* 8–9, 1–13
7. Torgerson, P.R. *et al.* (2015) World Health Organization estimates of the global and regional disease burden of 11 foodborne parasitic diseases, 2010: a data synthesis. *PLoS Med.* 12, e1001920
8. Krecek, R.C. and Waller, P.J. (2006) Towards the implementation of the 'basket of options' approach to helminth parasite control of livestock: emphasis on the tropics/subtropics. *Vet. Parasitol.* 139, 270–282
9. Brent, R.J. (2011) An implicit price of a DALY for use in a cost-benefit analysis of ARVs. *Appl. Econ.* 43, 1413–1421
10. Diel, R. *et al.* (2014) Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. *Eur. Respir. J.* 43, 554–565
11. Kirigia, J.M. and Mwabu, G.M. (2018) Haemorrhage of gross domestic product from disability-adjusted-life-years among 15–59 year olds in Kenya. *Int. Arch. Med.* 11, 20
12. Drake, T. (2014) Priority setting in global health: towards a minimum DALY value. *Health Econ.* 23, 248–252
13. Torgerson, P.R. (2018) zDALY: an adjusted indicator to estimate the burden of zoonotic diseases. *One Health* 5, 40–45
14. Bouwknegt, M. *et al.* (2018) Prioritisation of food-borne parasites in Europe 2016. *Euro. Surveill.* 23 (9),
15. Hald, T. *et al.* (2016) World Health Organization estimates of the relative contributions of food to the burden of disease due to selected foodborne hazards: a structured expert elicitation. *PLoS One* 11, e0145839
16. Conraths, F.J. *et al.* (2017) Potential risk factors associated with human alveolar echinococcosis: Systematic review and meta-analysis. *PLoS Negl. Trop. Dis.* 11, e0005801
17. Rossi, P. *et al.* (2016) The first meeting of the European Register of Cystic Echinococcosis (ERCE). *Parasit. Vectors* 9, 243

Letter

The Birth of Red Complex Plastids: One, Three, or Four Times?

Miroslav Oborník[1,2,*]

A substantial portion of eukaryotic phototrophs in terms of species diversity and ecological significance is represented by algae equipped with complex plastids surrounded by three or four envelope membranes, which are descendants of a rhodophyte (red alga). The question at which point(s) in the tree of life such complex plastids were acquired is still, and likely will ever be, subject of much discussion. Opinions on this issue vary from a single secondary endosymbiotic event at the root of chromalveolates or chromists (taxonomic groups composed of alveolates, stramenopiles, cryptophytes, and haptophytes) [1,2], to four independent secondary endosymbioses in each group of algae with red complex plastids, such as plastid-bearing alveolates, ochrophytes (photosynthetic stramenopiles), cryptophytes, and haptophytes [3], or even to complex sequences of serial and/or higher order endosymbiotic events (e.g., [4]). In spite of the speculative character of this topic, the common origin of stramenopile and alveolate plastids in a single secondary endosymbiotic event as reviewed by White and Suvorova in a recent issue of *Trends in Parasitology* [5], in my opinion is quite unlikely. Such an evolutionary scenario would require numerous independent losses of plastids in early branching stramenopiles (e.g., oomycetes, *Blastocystis*, labyrinthulomycetes, bicosoecids) as well as in alveolates (ciliates and *Acavomonas*). The loss of a plastid appears to be quite rare in the evolution of eukaryotes. So far only two instances of secondary plastid loss have been convincingly shown: in the lineage of apicomplexan parasites of the genus *Cryptosporidium* [6] and the closely related gregarines [7], and in the parasitic dinoflagellate *Haematodinium* [6]. While it seems to be difficult to lose the plastid once you have it, many algal lineages, including apicomplexan parasites, lost the ability to photosynthesize, which leaves them a relic nonphotosynthetic plastid in a secondarily heterotrophic cell. Such plastids are retained because essential biochemical pathways, that are lost from the host cell, take place in these plastids. Examples for such pathways are the heme pathway, nonmevalonate isoprenoid synthesis, fatty acid biosynthesis type II, and iron–sulfur cluster assembly in the apicomplexan plastid (apicoplast). However, it should be pointed out that although the lack of plastids in early branching heterotrophs in stramenopiles and alveolates is most likely a result of their primary heterotrophy, it can be also explained by early loss of plastids in their evolution: if the organelle were lost before it became essential for the host cell, it would very likely not leave many traces in the host genome [8]. This scenario cannot be rejected with certainty; however- because of numerous losses that would be needed to explain the absence of a plastid in the diverse early branching stramenopiles – it seems to be quite unlikely.

The origin of apicomplexan plastids is further complicated by the possible replacement of the original, presumably secondary, myzozoan (a group composed of dinoflagellates, chrompodellids, and apicomplexans) plastid by a tertiary endosymbiont (Figure 1), likely a stramenopile related to a eustigmatophyte alga [9]. Accumulating phylogenetic evidence based on plastid-encoded genes [9], genes coding for photosystems, cytochrome bf6 and plastid ATP synthase [10], as well as the pigment composition of plastids from chromerid algae, the closest known phototrophic relatives to Apicomplexa [9], supports this scenario. Also, the absence of chlorophyll *c*, the typical tetrapyrrole light-harvesting pigment of rhodophyte-derived complex plastids, defines to some extent the possible evolutionary link between stramenopiles and chromerids (and consequently apicomplexans), because all eustigmatophytes, a group of phototrophic stramenopiles, lack this pigment as well [11]. Recent evolutionary analysis of the diatom plastid proteome [12] suggests that this group of phototrophs contains tertiary plastids likely originating from a