Chapter 15
Burden and Risk Assessment of Foodborne Parasites

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Abbreviations

DALY	Disability-adjusted life year
FBP	Foodborne parasite
FERG	Foodborne Disease Burden Epidemiology Reference Group
GBD	Global Burden of Disease
MCDA	Multi-criteria decision analysis
MPRM	Modular process risk model
QMRA	Quantitative microbiological risk assessment

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Y.R. Ortega, C.R. Sterling (eds.), *Foodborne Parasites*, Food Microbiology and Food Safety, DOI 10.1007/978-3-319-67664-7_15

SMPH Summary measure of population health
YLD Years lived with disability
YLL Years of life lost

15.1 Preface

Burden and risk assessment play an increasingly important and accepted role in defining control policies for foodborne parasites (FBPs). Burden assessment is a top-down approach, starting from available epidemiological data, while risk assessment is a bottom-up or predictive approach, starting from exposure and dose-response data (Newsome et al. 2009; Stella et al. 2013). Both methods however share a common goal of generating estimates of the health and economic impacts of the concerned hazards. These estimates can be used to generate an evidence-based ranking of the impact of FBPs (i.e. risk ranking) and a baseline against which the effects of interventions can be evaluated (Devleesschauwer et al. 2014a). Risk assessment further provides a scientific framework for evaluating the potential effects of intervention measures and, by combining with economic models, the expected efficiency of such measures.

In this chapter we review methods for quantifying disease burden, for quantifying health risks and for ranking risks. We present applications to FBPs but acknowledge that these methods can be applied to any *hazard* (i.e. any biological, chemical or physical agent able to cause harm or adverse effects). Burden assessment is even more general, as it can also be applied to *outcomes* (such as diarrhoea or epilepsy) and *risk factors* (such as unsafe water or lack of sanitation).

15.2 Quantifying Disease Burden

15.2.1 Health Impact

Quantifying health impact may be based on disease occurrence (prevalence or incidence) or on the number of deaths (mortality). However, these *simple* measures of population health do not provide a complete picture of the impact of FBPs on human health (Batz et al. 2012; Devleesschauwer et al. 2015a). Indeed, while certain parasitic infections may be very common, their clinical impact may be limited. Infections with a highly prevalent parasite such as the pinworm, *Enterobius vermicularis*, for instance, have a very low burden because most of the cases are mild to asymptomatic and self-limiting (Knopp et al. 2012). Likewise, ignoring the age at which people die and thus not considering how many years of healthy life might be lost due to death results in not fully capturing the impact of mortality. Disease severity, defined by the impact on quality of life and the duration of the concerned symptoms, and the

life expectancy at the age of death should thus be accounted for when quantifying burden of disease. Furthermore, simple measures of population health do not combine the impacts of morbidity and mortality. This prohibits a comparative ranking of highly morbid but not necessarily fatal diseases, such as chorioretinitis due to congenital toxoplasmosis, and highly lethal diseases such as alveolar echinococcosis. The absence of a correct ranking complicates decisions on resource allocation priorities.

To overcome the limitations of simple measures such as incidence and mortality, *summary* measures of population health (SMPHs) have been developed as an additional source of information for measuring disease burden. The disability-adjusted life year (DALY) is currently the most widely used SMPH in public health research. Originally developed to quantify and compare the burden of diseases, injuries and risk factors within and across countries, the DALY summarises the occurrence and impact of morbidity and mortality in a single metric (Murray and Lopez 2013; Devleesschauwer et al. 2014b). The DALY is the key measure in the Global Burden of Disease (GBD) studies and is officially adopted by the World Health Organization for reporting on health information (Murray et al. 2012; WHO 2013).

The DALY is a health gap measure, measuring the healthy life years lost due to a disease or injury against some idealised health profile. DALYs are calculated by adding the number of years lived with disability adjusted for the severity of the disease (YLDs) and the number of years of life lost due to premature mortality (YLLs):

YLD = number of incident cases × duration until remission or death × disability weight

YLL = number of deaths × residual life expectancy at the age of death

An alternative formula for calculating YLDs was introduced by the GBD 2010 study (Murray et al. 2012):

YLD = number of prevalent cases × disability weight

This formula reflects a prevalence perspective instead of an incidence perspective. The incidence perspective assigns all health outcomes, including those in future years, to the initial event (e.g. exposure to a certain FBP). This approach therefore reflects the future burden of disease resulting from current events. In the prevalence perspective, on the other hand, the health status of a population is assessed at a specific point in time, and prevalent diseases are attributed to initial events that happened in the past. This approach thus reflects the current burden of disease resulting from previous events. Although both perspectives are valid, the incidence perspective is more appropriate for FBPs, because it is more sensitive to current epidemiological trends, including the effects of intervention measures (Murray 1994; Devleesschauwer et al. 2015a).

Different approaches can be taken for calculating DALYs, depending on whether the interest lies in quantifying the burden of a health outcome, a hazard or a risk factor (Devleesschauwer et al. 2014c). A natural choice for quantifying the health impact of FBPs is the *hazard-based* approach. This approach defines the burden of

Table 15.1 Health states associated with foodborne parasites, based on Havelaar et al. (2012), Devleesschauwer et al. (2015a) and Torgerson et al. (2015)

Foodborne parasite	Health state
Cryptosporidium spp.	Diarrhoeal disease
Entamoeba spp.	Diarrhoeal disease
Giardia spp.	Diarrhoeal disease, postinfectious irritable bowel syndrome
Toxoplasma gondii	Congenital toxoplasmosis: intracranial calcification, hydrocephalus, chorioretinitis, central nervous system abnormalities; acquired toxoplasmosis: acute fever-like illness, post-acute illness, chorioretinitis
Ascaris spp.	Ascariasis infestation, abdominopelvic problems, wasting
Trichinella spp.	Acute trichinellosis: diarrhoea, facial oedema, myalgia, fever, headache
Echinococcus granulosus	Cystic echinococcosis: pulmonary, hepatic, central nervous system problems
Echinococcus multilocularis	Alveolar echinococcosis: abdominopelvic problems
Taenia solium	Epilepsy, chronic headache, hydrocephalus
Foodborne trematodes	Abdominopelvic, central nervous system, pulmonary problems

a specific FBP as that resulting from the health states, i.e. acute symptoms, chronic sequelae and death, that are causally related to the concerned parasite transmitted through food and which may become manifest at different time scales or have different severity levels (Mangen et al. 2013). The starting point for quantifying DALYs is therefore typically the construction of a *disease model* or outcome tree, which is a schematic representation of the various health states associated with the concerned hazard, and the possible transitions between these states (Devleesschauwer et al. 2014c).

Table 15.1 shows selected causally related health states for ten important FBPs, highlighting the diverse nature of symptoms and sequelae linked to FBPs (Havelaar et al. 2012; Devleesschauwer et al. 2015a; Torgerson et al. 2015).

Disease burden can be calculated at different levels, ranging from the global to the individual level. Recently, the Foodborne Disease Burden Epidemiology Reference Group (FERG) of the World Health Organization quantified the *global* burden of foodborne disease (Havelaar et al. 2015), including FBPs (Torgerson et al. 2015). Several authors have estimated the burden of FBPs at *country level* to support national decision-making (Polinder et al. 2012). Recently, Trevisan et al. (2017) estimated that in Tanzania, *Taenia solium* neurocysticercosis results in nearly 20,000 new cases of epilepsy per year, leading to over 200 deaths and over 30,000 DALYs. Some studies also include burden estimates at the *individual level*, i.e. the number of DALYs per case. Figure 15.1 contrasts the population and individual level burden of three FBPs in Nepal, highlighting the importance of congenital toxoplasmosis at both levels (Devleesschauwer et al. 2014d).

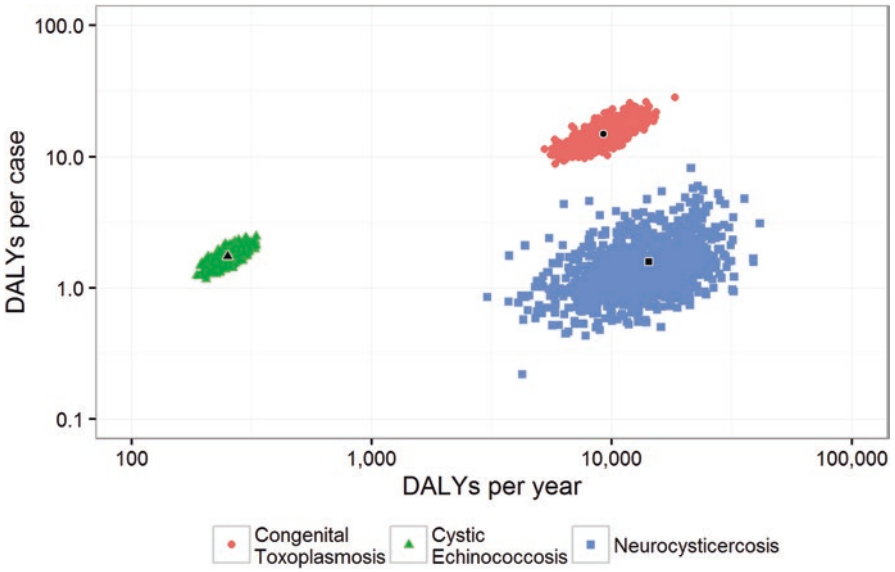

Fig. 15.1 Population level (x axis) versus individual level (y axis) disease burden of three foodborne parasites in Nepal (Adapted from Devleesschauwer et al. 2014d)

15.2.2 Economic Impact

As for health impact, different approaches exist for estimating the economic impact of FBPs. The most commonly applied approach measures the *cost of illness* from a societal perspective, taking into account that FBPs have an impact on several stakeholders in the society (Mangen et al. 2015). In cost-of-illness studies, a distinction is typically made between direct and indirect costs on the one hand and healthcare and non-healthcare cost on the other hands (Mangen et al. 2010). *Direct healthcare costs* are related to the resources provided by the healthcare sector, such as healthcare provider consultations, diagnosis, medication and hospitalisation. *Direct non-healthcare costs* are related to the resources used for healthcare that are not born by the healthcare system, such as over-the-counter medications and other patient copayments, and travel expenses to visit a healthcare provider. *Indirect non-healthcare costs* include productivity losses due to absenteeism or job loss of patients and their caregivers. *Indirect healthcare costs*, finally, are related to medical consumption in life years gained due to life-saving or death-postponing interventions (van Baal et al. 2011) but are rarely included in cost-of-illness studies.

In Tanzania, the cost of illness of epilepsy due to *Taenia solium* neurocysticercosis was estimated at over 5 million USD, with over 90% due to inactivity-related indirect costs (Trevisan et al. 2017). In the Netherlands, the cost of illness of *Cryptosporidium* spp., *Giardia* spp. and *Toxoplasma gondii* was €8 million, €11

million and €55 million, respectively, accounting for 16% of the economic impact of all considered foodborne pathogens (Mangen et al. 2015). Indirect non-healthcare costs were the most important component of *Cryptosporidium* spp. and *Giardia* spp. cost of illness, while direct healthcare costs were the dominant component of the cost of illness of *T. gondii*.

In addition to the costs linked to their health impact, FBPs may incur an economic impact due to surveillance and other regulatory activities in place to monitor and prevent infection. In the EU, for instance, surveillance of pigs at slaughterhouse level for *Trichinella* spp. induces an estimated annual cost of €25 million (Torgerson 2013), while the health impact of trichinellosis is negligible (Devleesschauwer et al. 2015b). As many FBPs are zoonotic, livestock production losses due to clinical or subclinical infection further add to the economic burden. In Tanzania, the impact of lower prices for infected pigs was estimated at 2.8 million USD, accounting for 35% of the total economic impact of *T. solium* in the country (Trevisan et al. 2017).

Although FBPs are of global concern, there are relatively few assessments of their global economic impact. Budke et al. (2006) estimated global monetary losses resulting from human and livestock cystic echinococcosis. Human-associated direct and indirect costs resulted in a global loss of 764 million USD, while livestock-associated losses due to liver condemnation and reductions in carcass weight, hide value, milk production and fecundity resulted in a global loss of 2 billion USD. Murrell (1991), Roberts et al. (1994) and Torgerson and Macpherson (2011) reviewed the economic impact of FBPs in selected countries.

15.3 Quantitative Microbiological Risk Assessment

Risk is defined by the Codex Alimentarius Commission as a function of the probability of an adverse effect consequential to a hazard in food and the severity of that effect (CAC 1999). Following this definition, integrative disease burden metrics such as DALYs and cost of illness are the most appropriate metrics for quantifying risk (Mangen et al. 2007). Nevertheless, risk is often expressed by simple metrics such as incidence of exposure or illness. Risk assessment is the scientific process that aims to examine this risk, in either a qualitative or quantitative way. Qualitative risk assessment results in nonnumerical risk estimates such as "negligible" or "high" risk or in semi-quantitative risk estimates (Ross and Sumner 2002; Newsome et al. 2009). Such models are typically simple and quick to implement but include several subjective steps and do not allow for a full quantification of uncertainty and variability (WHO/FAO 2009). The remainder of this section will therefore focus on quantitative risk assessment. Quantitative microbiological risk assessment (QMRA) aims to quantify the human health effects resulting from exposure to microbiological hazards including parasites, viruses, fungi, bacteria and their toxins. In contrast to chemical risk assessment, QMRA is a relatively young research field, with the emergence of applications to waterborne pathogens in the early 1990s (Rose et al. 1991) and to foodborne pathogens in the mid-1990s (WHO/FAO 2009). Current

QMRA methods are able to consider the uncertainties and variability inherent to any available information and propagate these to the final risk estimate, thus providing an objective scientific basis for decision-making (Lammerding and Paoli 1997). As a result, QMRA methods are increasingly promoted at national and international level to safeguard public health and facilitate free trade (Schroeder et al. 2007), especially in areas of water quality (Macler and Regli 1993) and food safety (Stella et al. 2013). Following the trend towards risk-based standards for foodborne pathogens, the Codex Committee on Food Hygiene explicitly calls for a risk-based approach in their guidelines for the control of *Trichinella* spp. and *Taenia saginata* in meat (FAO/WHO 2014).

QMRA fits into a larger process of risk analysis (Fig. 15.2), which is further characterised by *risk management* (i.e. the identification, selection and implementation of control policies) and *risk communication* (i.e. the mutual interaction between scientists, risk managers and the general public). QMRA itself is classically divided in four components (Fig. 15.2; Buchanan 1998; CAC 1999; Lammerding and Fazil 2000; Buchanan et al. 2000). *Hazard identification* is the process of identifying the biological hazards capable of causing adverse health effects following exposure, as well as the nature of these adverse health effects. *Exposure assessment* is the evaluation of the likely intake of the biological agent via relevant exposure routes. *Dose-response assessment* (the quantitative form of hazard characterisation) is the evaluation of the functional relationship between the ingested dose and the probability of an adverse response, such as infection, illness or death. *Risk characterisation*, finally, is the estimation of the probability of occurrence and severity of the

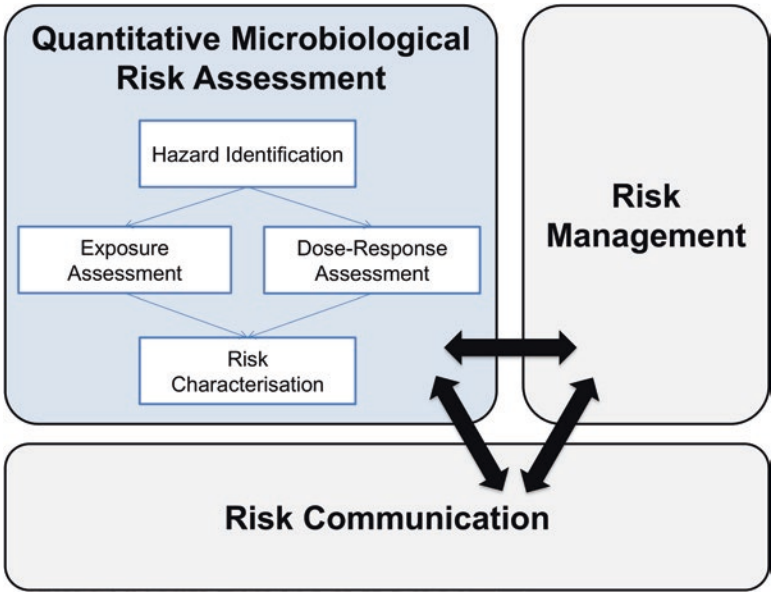

Fig. 15.2 Risk analysis framework for microbiological hazards

potential adverse health effects in a population, based on the results of the preceding three components.

15.3.1 Hazard Identification

Hazard identification is the first step in a formal risk assessment and aims to identify which hazards are present in the food and which adverse health effects they are able to cause. This activity is therefore mainly a qualitative review of available information. The main focus of hazard identification is typically to determine which health states are causally related to the concerned hazards, thus corresponding to the disease models used in disease burden quantifications. This assessment is less involved for FBPs than, for example, chemicals, as the cause-and-effect relationship can typically be observed in individual cases, allowing for categorical attribution. For instance, a case of diarrhoea can be attributed to *Giardia* spp. if a high number of cysts are observed in the stool, or a case of epilepsy can be attributed to *Taenia solium* neurocysticercosis if cysticerci are witnessed in the brain.

However, when the FBP elevates the risk of a disease that occurs in the population from other causes as well, attribution can only be made at a population level and not on an individual basis. This is the case for certain chronic sequelae that may be linked to FBPs, such as irritable bowel syndrome, *Giardia* spp., schizophrenia and *Toxoplasma gondii*. As a result, there is considerably more uncertainty and debate, surrounding these causal relationships. When categorical attribution is not feasible, a valid approach for quantifying the association between exposure and outcome is to use a counterfactual analysis in which the current disease outcomes with current exposure are compared to the disease outcomes under an alternate exposure scenario (e.g. a minimum risk exposure which could be zero or some accepted background level; Prüss-Üstün et al. 2003). This allows for the calculation of a population attributable fraction or population attributable risk, which is a measure of the association between exposure and outcome at the population level. Estimates of the population attributable fraction for *Toxoplasma gondii*-associated schizophrenia, for instance, ranged between 9% (Torgerson et al. 2015) and 21% (Smith 2014).

15.3.2 Exposure Assessment

Exposure assessment aims to evaluate the expected dose, d, of the ingested hazard (WHO/FAO 2008). Under the assumption of independence, this dose can be obtained as the product of the concentration of the hazard in the ingested medium (e.g. meat, water, aerosol, etc.), μ, and the amount of medium consumed, m. Typically, the concentration μ of the hazard in the medium is not exactly known but must be estimated from random samples from the medium of interest, in which the

concentration, count or the presence/absence of the hazard is measured. By fitting parametric models to these external data sources, the concentration in the medium, μ, can be estimated (Haas et al. 2014). Unless the point of consumption is the only interest, exposure assessment should also describe the relevant exposure pathways along the farm-to-fork chain and the different processes that affect the probability and level of exposure of the consumed end product (WHO/FAO 2008).

15.3.2.1 Exposure Assessment from Concentration Data

Different parametric models may be appropriate to describe the concentration μ of a FBP. In general, any non-negative continuous probability distribution function may be a possible model. In literature, the most commonly applied distribution has been the log-normal model. Alternative models are the gamma, Weibull, inverse Gaussian (aka Wald) and generalised inverse Gaussian model (Haas et al. 2014).

Depending on the analytical sensitivity of the test, assays may exhibit a certain detection limit or lowest measurable concentration. Samples for which the true concentration is below this detection limit are called below-detection-limit samples. Such samples are an example of left-censored data and require adapted statistical approaches (Haas et al. 2014).

15.3.2.2 Exposure Assessment from Count Data

Count assays provide the most informative data for estimating hazard concentrations, reporting both the number of organisms detected in the sample and the sample quantity (e.g. volume, weight, surface area, etc.), which may differ across samples. Haas and Rose (1996), for instance, presented *Cryptosporidium* oocyst counts from a water supply in the United States. Samples were collected once a week over a one-year study period, with sample volumes ranging from 18 to 227 litres. Surveillance of *Trichinella* spp. in pigs may be done by artificial digestion of a pooled sample of 1 g diaphragm pillar meat from each of 100 pigs, quantifying exposure as the number of larvae in a sample of 100 g (Commission Regulation (EC) No 2075/2005).

The most basic assumption to model μ from count data is that the distribution of hazards in the sample follows a Poisson distribution with mean μV, implying that the hazard is distributed randomly in the medium. Under the Poisson model, the probability that a sample of quantity V contains k organisms is given by:

$$P_P\left(x=k\right)=\frac{\left(\mu V\right)^k}{k!}\exp\left(-\mu V\right)$$

Alternative models relax the Poisson assumption of randomness and account for extra-Poisson variability. Such models are discrete mixture distributions $P_M(x)$ of the general form:

$$P_M\left(x=k\right)=\int_k^0 P_P\left(x=k|\mu V\right)h\left(\mu|\beta\right)d\mu$$

in which $P_P(x = k)$ is a Poisson model and $h(\mu)$ is a non-negative continuous probability density function describing the variability in μ, as described above. Assuming a gamma model for the mean concentration μ leads to a negative binomial model for the counts, while the other models presented above would lead to a Poisson log-normal, Poisson-Weibull, Poisson-inverse Gaussian and Poisson-generalised inverse Gaussian model, respectively (Haas et al. 2014; Jongenburger et al. 2012). Except for the Poisson log-normal and Poisson-Weibull model, analytical solutions exist for these hierarchical mixture models (Haas et al. 2014). Bayesian methods allow modelling these hierarchies explicitly, hereby avoiding the need for an analytical solution.

15.3.2.3 Exposure Assessment from the Presence/Absence Data

Dilution or titration assays report the presence or absence of the hazard in a certain quantity of the concerned medium. Letting y denote the presence/absence of the hazard, the probability of observing the hazard in the sample can be modelled as a Bernoulli process:

$$P\left(y\right)=\pi^y\left(1-\pi\right)^{1-y}$$

where π is the probability that the sample contains one or more organisms, $P(k \geq 0) = 1 - P(k = 0)$. Again, if we assume a Poisson model to describe the occurrence of organisms in the sample, this yields $P(k = 0) = \exp(-\mu V)$. The probability of observing the hazard in the sample is therefore given by the following Bernoulli-Poisson mixture model:

$$P\left(y\right)=\left(1-\exp\left(-\mu V\right)\right)^y\left(\exp\left(-\mu V\right)\right)^{1-y}$$

15.3.2.4 Farm-to-Fork Pathway Models

Exposure assessment often requires a description of the pathway from production to consumption. Indeed, microbiological hazards can enter foods at many points in the chain, and their prevalence and concentration may change along the chain. The transmission of pathogens along a farm-to-fork pathway may be modelled using mathematical models in which the output of the previous step is the input of the next step. To formalise this idea, Nauta (2008) introduced the *modular process risk model* (MPRM), which models the food pathway as a sequence of well-defined modules. Each module corresponds to one-*process step*, which in term is defined by

one or more *basic processes*. These basic processes can be *product handling processes*, such as mixing, partitioning, removal and cross-contamination, or *microbiological processes*, such as growth and inactivation. To support the modelling of microbiological processes, an online database of microbial growth and survival curves, *ComBase*, has been developed (Baranyi and Tamplin 2004).

In a QMRA model for *Toxoplasma gondii* in the Netherlands, Opsteegh et al. (2011) used bradyzoite concentration and portion size data to estimate the bradyzoite number in infected unprocessed portions for human consumption. To estimate the number of bradyzoites per processed portion, they applied reduction factors for salting, freezing and heating (i.e. corresponding to the microbiological process of inactivation). Guo et al. (2015) estimated the exposure risk to *T. gondii* from various meat products consumed in the United States based on a qualitative farm-to-retail pathway model. The included modules were farm, abattoir, storage and transportation, meat processing, packaging and retail, with two product handling processes, i.e. removal and cross-contamination, considered in the different modules.

15.3.3 Dose-Response Assessment

The dose-response assessment, also referred to as the quantitative component of hazard characterisation, aims to describe the relationship between the ingested dose of the hazard and the extent of the associated adverse health effects (Buchanan et al. 2000). The dose-response relationship for microbiological hazards shows some essential differences with that of chemical hazards.

First, a clear distinction needs to be made between infection and illness. In QMRA, infection is defined as the invasion (and multiplication) of the microbiological hazard in the host and the reaction of the host to these events. Infection may be ascertained by the detection of the hazard in the host's tissues, secreta or excreta or by detecting antibodies against the hazard. Infection does not necessarily lead to disease and may remain asymptomatic. Whether or not illness develops depends on the balance between the hazard's virulence and infectivity and the host's susceptibility. In severe cases, illness will be followed by death. Unlike for chemical hazards, it is postulated that even one microbiological organism is sufficient to cause illness, even though the likelihood of illness increases with increasing numbers of ingested hazards (Teunis and Havelaar 2000).

A second important distinct feature of the dose-response assessment step for microbiological hazards is the type of data typically used to establish dose-response curves, i.e. human feeding trials or outbreak data (Mena 2006). Extrapolation of animal studies for determining dose-response is less commonly applied, in contrast to chemical risk assessment. In feeding trials, participants are given a range of doses (through ingestion, inhalation or direct contact), and a human health endpoint of interest (infection and/or illness) is determined. Typically, due to ethical constraints, healthy adults are used, and a relatively high amount of (low virulent) dose is administered to be able to use as few participants as possible but still observe the

adverse event. However, in typical contamination situations, people will be exposed to lower doses of (more virulent) hazards. An important issue in dose-response modelling is therefore the prediction of the probability of the adverse health effect in low-dose ranges (Havelaar and Swart 2014).

A third distinct feature is that microbiological organisms are distinct or discrete particles, which is accounted for when constructing dose-response models. Finally, unlike chemical hazards, repeated exposures may induce acquired immunity, thereby reducing the risk of infection and/or illness (Havelaar and Swart 2014).

15.3.3.1 Dose-Infection Models

Different models have been proposed to model the relationship between exposure and infection. It is common in QMRA literature to distinguish between *mechanistic* models, which have a biological basis, and *empirical* models, for which no biological basis is apparent (Buchanan et al. 2000).

Currently, the exponential and Beta-Poisson models, both introduced by Haas (1983), are recommended for foodborne and waterborne hazards (Schroeder et al. 2007). Both models are mechanistic models, derived from a biological reasoning underlying the relationship between dose and infection. This biological process is assumed to consist of distinct sequential steps. First, a host must ingest one or more viable hazard. Then, some of these ingested hazards must survive the host defences and multiply to cause infection. Further assumptions can be made about the minimum number of surviving organisms $k_{\min}$ needed to initiate infection. Models in which $k_{\min} = 1$ are called *single-hit models*. Empirical evidence shows that, under certain circumstances, single hazards are indeed able to cause infection; a single viable egg of *Echinococcus* can, for instance, cause infection and disease (Gemmell 1990). Hence, the common consensus is to derive mechanistic dose-infection models that are single-hit models. However, for nematodes such as *Trichinella* spp., there must be at least one male and one female survivor to initiate infection, requiring adapted modelling approaches (Teunis et al. 2012).

The exponential dose-response model assumes that the ingested doses among exposed hosts are Poisson distributed and that each ingested hazard is associated with an equal, independent probability of initiating a response:

$$\Pr\left(\text{infection}|\text{dose}\right) = 1 - \exp\left(-rd\right),\ r > 0$$

where d is the ingested dose and r is a rate parameter equal to the probability of a single organism initiating a response.

Messner and Berger (2016) extended the basic exponential dose-response model with a parameter π reflecting the susceptible fraction of human hosts, leading to an exponential *with immunity* model:

$$\Pr\left(\text{infection}|\text{dose}\right) = \pi\left(1 - \exp\left(-rd\right)\right),\ r > 0,\ 0 < \pi < 1$$

When r is assumed to equal 1, i.e. each hazard is capable of initiating infection, this model reduces to a fractional Poisson model, which is also the probability of exposure given an average dose d:

$$\Pr\left(\text{infection}|\text{dose}\right) = \pi\left(1-\exp\left(-d\right)\right),\ 0<\pi<1$$

In the Beta-Poisson model, ingested doses are assumed to be Poisson distributed as well, but now the probability that an individual organism initiates a response is assumed to follow a Beta distribution. As a result, the Beta-Poisson model allows to characterise variability of the host-pathogen survival probability. The exact Beta-Poisson model is given by:

$$\Pr\left(\text{infection}|\text{dose}\right) = 1-{}_1F_1\left(\alpha,,\alpha+\beta,,-d\right),\ \alpha>0,\ \beta>0$$

where ${}_1F_1$ denotes the Kummer confluent hypergeometric function and α and β are the parameters of the Beta distribution. Furumoto and Mickey (1967) proposed an approximation to the confluent hypergeometric function, resulting in the more commonly used approximate Beta-Poisson model:

$$\Pr\left(\text{infection}|\text{dose}\right) = 1-\left(1+d/\beta\right)-\alpha,\ \alpha>0,\beta>0$$

For many datasets where $\beta \gg 1$ and $\alpha \ll \beta$, the differences between the approximation errors provided by applying the approximate Beta-Poisson as compared to those of the hypergeometric function are negligible. However, Teunis and Havelaar (2000) showed that this approximation is in fact not a single-hit model and that it becomes problematic at low doses when the assumptions postulated by Furumoto and Mickey (1967) are not met. Furthermore, even when the most likely values of α and β do satisfy the conditions, the assumptions may not be met for every individual pair of parameter samples in the uncertainty set. Therefore, they promote the use the exact Beta-Poisson model.

In addition to the mechanistic models, various so-called empirical models are used to describe the relationship between ingested dose and expected response (Buchanan et al. 2000). These models do not arise from biological reasoning but follow the logic that the probability of a response should be zero at dose zero, reach one when dose becomes very high and increase monotonically in between. These are properties of sigmoidal functions, including cumulative distribution functions. Some of the empirical models described in literature are the log logistic, log probit, extreme value, Weibull and gamma-Weibull model (Haas et al. 2014; Holcomb et al. 1999).

15.3.3.2 Dose-Illness Models

In contrast to dose-infection models, less work has been performed on models describing the relationship between dose and onset of *illness*. Historically, researchers have assumed that the probability of illness following infection is independent

of the dose (Rose et al. 1991; Haas et al. 1993; Haas and Rose 1996). Under this assumption, the probability of illness given dose can be factorised as follows:

$$\Pr(\text{illness}|\text{dose}) = \Pr(\text{illness}|\text{infection})\Pr(\text{infection}|\text{dose})$$

Pouillot et al. (2004), for instance, modelled the probability of illness following *Cryptosporidium* spp. infection in the immunocompetent as a Beta (9,11) distribution, which has a mean of 45%. For the immunocompromised, they assumed a probability of illness of 100%.

In general, however, the dose-illness relationship is given by Namata et al. (2008):

$$\Pr(\text{illness}|\text{dose}) = \Pr(\text{illness}|,\text{infection}|,\text{dose})\Pr(\text{infection}|\text{dose})$$

According to Teunis et al. (1999), the probability of illness given infection and dose can in theory follow any of three distinct shapes, i.e. increasing, decreasing or constant. When the probability of illness is increasing, the resulting dose-illness relationship has a similar shape as the dose-infection models, so that these models can be applied to model dose-illness. A general empirical framework for modelling all possible dose-illness relationships has been proposed by Namata et al. (2008) and Bollaerts et al. (2008), who used fractional polynomials and generalised linear mixed models to model dose-illness relationships for *Campylobacter* and *Salmonella*. So far little work has been done on mechanistic dose-illness models, especially not for FBPs. Buchanan et al. (2000) presented a mechanistic dose-illness model composed of three compartments, i.e. gastric acidity barrier, attachment/infectivity and morbidity/mortality. Havelaar and Swart (2014) discussed dose-illness models that can incorporate both the effects of dose-dependency and acquired immunity in the probability of illness given infection.

15.3.3.3 Dose-Response Models for Foodborne Parasites

Table 15.2 provides an overview of proposed dose-response models for FBPs. To date, most dose-response assessments of FBPs have focused on intestinal protozoa, particularly *Cryptosporidium* spp., and were typically performed in the context of waterborne transmission. Recently, dose-response models have been introduced for *Toxoplasma gondii* and for macroparasites such as *Ascaris lumbricoides* and *Trichinella* spp.

Information on *Cryptosporidium* spp. dose-response first became available from three feeding studies in healthy human volunteers initiated in 1993 at the University of Texas (DuPont et al.1995) ; Chappell et al. 1999); Okhuysen et al. 1999). These studies used three distinct *Cryptosporidium parvum* isolates, referred to as the Iowa, TAMU and UCP strains. Messner et al. (2001) fitted exponential dose-response models to these datasets and performed a random effect meta-analysis of the three

Table 15.2 Estimated dose-response models for foodborn parasites

Foodbome parasite	Response	Model	Reference
Cryptosporidium parvum, Iowa strain	Oocyst detection	Exponential ($\hat{r}$ = 0.00419)	Teunis et al. (1999)
Cryptosporidium parvum, Iowa strain	Clinical definition of infection	Exponential ($\hat{r}$ = 0.00526)	Messner et al. (2001) and Teunis et al. (2002a)
Cryptosporidium parvum, Iowa strain	Clinical definition of infection	Hypergeometric ($\hat{\alpha}$ = 0.801, $\hat{\beta}$ = 56.24)	Teunis et al. (2002a)
Cryptosporidium parvum, Iowa strain; immunocompromised mice	Oocyst detection	Exponential ($\hat{r}$ = 0.354)	Pouillot et al. (2004)
Cryptosporidium parvum, TAMU strain	Clinical definition of infection	Exponential ($\hat{r}$ = 0.0573)	Messner et al. (2001) and Teunis et al. (2002a)
Cryptosporidium parvum, TAMU strain	Clinical definition of infection	Hypergeometric ($\hat{\alpha}$ = 1.831, $\hat{\beta}$ = 18.06)	Teunis et al. (2002a)
Cryptosporidium parvum, UCP strain	Clinical definition of infection	Hypergeometric ($\hat{\alpha}$ = 1.17e−5, $\hat{\beta}$ = 8.15e−6)	Teunis et al. (2002a)
Cryptosporidium spp., pool of seven datasets	Clinical definition of infection	Exponential with immunity ($\hat{\neq}$ = 0.737, $\hat{r}$ = 0.608)	Messner and Berger (2016)
Cryptosporidium spp., pool of seven datasets	Clinical definition of infection	Fractional Poisson ($\hat{\neq}$ = 0.737)	Messner and Berger (2016)
Cryptosporidium spp., pool of seven datasets	Clinical definition of infection	Beta-Poisson ($\hat{\alpha}$ = 0.116, $\hat{\beta}$ = 0.121)	Messner and Berger (2016)
Giardia spp.	Cyst excretion	Exponential ($\hat{r}$ = 0.0198)	Rose et al. (1991)
Toxoplasma gondii, type II; mice	Bioassay positive	Exponential ($\hat{r}$ = 0.001535)	Dubey (1997), Derouin et al. (2005), Opsteegh et al. (2011), and Guo et al. (2015)
Toxoplasma gondii, type II; mice, with scaling factor	Bioassay positive	Exponential ($\hat{r}$ = 0.001535 × 0.005)	Guo et al. (2015)
Toxoplasma gondii, type II; mice	Bioassay positive	Beta-Poisson ($\hat{\alpha}$ = 1.479, $\hat{\beta}$ = 582.4)	Guo et al. (2015)

(continued)

Table 15.2 (continued)

Foodbome parasite	Response	Model	Reference
Toxoplasma gondii, type II; mice, with scaling factor	Bioassay positive	Beta-Poisson ($\hat{\alpha}$ = 1.479, $\hat{\beta}$ = 582.4/0.003)	Guo et al. (2015)
Ascaris lumbricoides; exposure through crops	Egg excretion	Beta-Poisson ($\hat{\alpha}$ = 0.104, $\hat{\beta}$ = 1.096)	Navarro et al. (2009)
Ascaris lumbricoides; exposure through soil	Egg excretion	Beta-Poisson ($\hat{\alpha}$ = 0.104, $\hat{\beta}$ = 0.044)	Navarro et al. (2009)

datasets, highlighting the important heterogeneity between the three involved strains. Teunis et al. (2002a) fitted exponential and hypergeometric dose-response models to the individual and pooled datasets and developed a two-level dose-response model to simultaneously model the heterogeneity between and within isolates. By including the IgG level as a covariate in the single-hit model, they further explored the effect of immunity on the relationship between dose and infection or acute illness (Teunis et al. 2002b). Recently, Messner and Berger (2016) compiled seven human challenge dose-response studies for *Cryptosporidium* spp., including five studies using *C. parvum* and one each using *Cryptosporidium hominis* and *Cryptosporidium muris*. The best fitting models indicated that human susceptibility may be a more important source of heterogeneity than virulence differences. Pouillot et al. (2004), finally, proposed an exponential dose-response model for the immunocompromised, based on a feeding study in immunocompromised mice.

The only *Giardia* spp. dose-response model available in literature is given by Rose et al. (1991). They fitted an Exponential dose-response model to data from human feeding studies published in the 1950s. As noted by Teunis et al. (1999), these results indicated a high single-hit probability of infection but, as none of the infected persons developed gastroenteritis, did not provide any information on the probability of illness.

In a QMRA for meat-borne *Toxoplasma gondii* infection in the Netherlands, Opsteegh et al. (2011) used an exponential dose-response model established for *T. gondii* type II in mouse experiments (Dubey 1997); Derouin et al. 2005). Guo et al. (2015) found that this dataset was reasonably well explained by the exponential dose-response model and less so by the Beta-Poisson dose-response model. They also computed scaling factors so that these mouse-derived models could predict *T. gondii* infection in humans.

Schönning et al. (2007) and Machdar et al. (2013) modelled the dose-response relationship of *Ascaris lumbricoides* as an exponential model with $r = 1$, corresponding to the maximum risk curve (Teunis and Havelaar 2000). Navarro et al. (2009) estimated a Beta-Poisson dose-response model for *A. lumbricoides*, by combining *A. lumbricoides* infection rates from the Mezquital Valley in Mexico with data on *Ascaris* egg concentrations in crops and soil.

Takumi et al. (2009) and Teunis et al. (2012) analysed nine published outbreaks of human trichinellosis to determine the dose-response of *Trichinella* spp. in humans, using seroconversion as response outcome. They extended the Beta-Poisson dose-response model by allowing for extra-Poisson variation in the ingested dose and by taking into account that both male and female worms need to be ingested to initiate infection. Their model resulted in a single-hit infection probability of around 1%.

15.3.4 Risk Characterisation

Risk characterisation is the final stage of QMRA and generates an estimate of the likelihood and extent of the adverse health effects a population will experience due to concerned hazard. This is achieved by integrating exposure and dose-response assessments, where the outcomes of the former analysis serve as an input to the latter analysis (Buchanan et al. 2000).

A crucial aspect of risk characterisation is the proper reflection of the level of confidence in the final risk estimates. In this context, the identification and quantification of uncertainty and variability play an important role, as well as a clear articulation of all assumptions and their support. Uncertainty relates to a lack of knowledge about the system (i.e. model uncertainty) or the parameters characterising the system (i.e. parameter uncertainty). Uncertainty can be mitigated by gaining knowledge, e.g. by collecting information on a larger sample size. Variability on the other hand relates to the stochastic nature of the system and cannot be reduced by increasing the sample size.

In earlier years, uncertainty was explored through scenario or one-way sensitivity analyses, generating, for instance, an average, conservative and worst-case risk estimate (Jaykus 1996). Improvements in computational power have now resulted in Monte Carlo or Latin hypercube simulation methods becoming the standard approach for propagating parameter uncertainty. In brief, these methods simulate random draws from probability distributions reflecting the uncertainty in the input parameters and use these random draws to establish a distribution of plausible risk estimates. Two-dimensional Monte Carlo methods may furthermore be used to additionally, but separately, capture the effects of variability (Miconnet et al. 2005; Pouillot and Delignette-Muller 2010).

Recently, Bayesian methods are increasingly used in QMRA to propagate parameter uncertainty (Delignette-Muller et al. 2006; Smid et al. 2010; Williams et al. 2011). With increasing computational power, Bayesian models may now be developed to capture the often complex processes leading to human exposure (Greiner et al. 2013; Schmidt et al. 2013).

A variety of software tools are being applied in the context of QMRA, some of which specifically developed for the purpose of risk assessment. To date, the most comprehensive tool for QMRA is FDA-iRisk, a web-based quantitative risk

assessment system to estimate and compare the risk of foodborne illness from microbial and chemical hazards (Chen et al. 2013). iRisk integrates seven model elements, i.e. definition of foods, hazards and population groups; process models (cf. MPRM); consumption models; dose-response models; and health outcomes (with default DALY per case values for selected hazards). The different model inputs are integrated through Monte Carlo simulations to quantify variability in the resulting risk estimates.

Other QMRA tools are dedicated to risk characterisation, exposure assessment or dose-response assessment. Risk characterisation is often performed in **Excel** with the add-on **@RISK**, which provides random number generators for a variety of probability distributions and functionalities for sensitivity analysis and plotting. Other add-ons, such as **PopTools**, **Ersatz** and **Crystal Ball**, provide similar features. **Analytica** is a visual software environment for the quantitative analysis of influence diagrams, which may also be applied in the context of QMRA. Other analysts developed models in general scientific software environments such as **R**, **SAS** and **MATLAB** (WHO/FAO 2008). Several **R** packages provide specific QMRA functions, e.g. **mc2d**, which is dedicated to two-dimensional Monte Carlo (Pouillot and Delignette-Muller 2010) and **fitdistrplus**, which allows fitting univariate models to (possibly censored) data.

15.4 Risk Ranking

In a time of increasing (recognised) threats and decreasing financial resources, there is a growing need to rationally allocate available means. Consequently, risk ranking is increasingly used within the food safety risk analysis framework (Stella et al. 2013). The aim of these exercises is to prioritise for decision-making certain hazards, hazard-commodity pairs or exposure routes for a given hazard, based on their perceived importance. As different stakeholders have their own prioritisation objectives and beliefs, the outcome of such exercises is necessarily context dependent. Consequently, there is no unique or intrinsically correct ranking of risks.

The main purpose of burden and risk assessments is often to rank different hazards according to the health or economic impact. Figure 15.3 shows the FERG ranking of FBPs according to their global health impact, quantified in terms of DALYs (Torgerson et al. 2015).

Using a single criterion to rank risks may however be insufficient as diseases vary greatly in incidence, clinical manifestations, control measures, transmission potential and socio-economic impact in animals and humans. *Trichinella* spp., for instance, have a near negligible health impact in Europe, while their economic impact remains important due to continuous monitoring and trade implications (Devleesschauwer et al. 2015b). It may therefore be required to base the ranking of risks on multiple criteria (Mangen et al. 2010). To quantify the disease burden of various foodborne hazards in the Netherlands in 2011, Mangen et al. (2015)

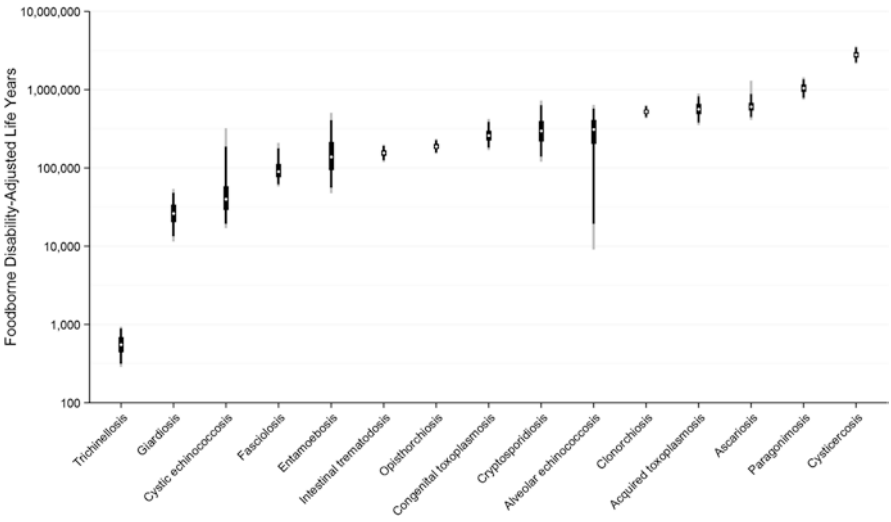

Fig. 15.3 Disability-adjusted life year-based global ranking of foodborne parasites according to Torgerson et al. (2015)

calculated DALYs and cost-of-illness estimates, both at the population and individual level. The different criteria led to different rankings, with some hazards scoring high on multiple criteria.

Ideally, however, a risk ranking exercise should result in a single ranking taking into account multiple criteria. Some authors combined DALYs and economic impact estimates by assuming one DALY to correspond to an economic loss equal to the per capita gross national product (Torgerson et al.(2008). This approach belongs to the family of *multi-criteria decision analysis* (MCDA) methods. In MCDA, an overall importance measure is constructed based on different criteria, which are assigned weights reflecting their perceived contribution (Cardoen et al. 2009; Havelaar et al. 2010; FAO/WHO 2014; Robertson et al. 2015). As these weights imply a normative choice, the definition of weights should reflect social preferences or expert opinion. The selection of criteria to be scored typically depends on expert opinion. The (quantitative, semi-quantitative or qualitative) scoring of the criteria can be based on existing data or on expert elicitation. Despite its subjective perfume, MCDA provides a transparent and consistent framework for ranking risks (Anderson et al. 2011). It also allows including criteria for which no quantifications are available or possible. In the joint Food and Agriculture Organization of the United Nations and World Health Organization multi-criteria-based ranking of FBPs, trade relevance and impacts on economically vulnerable communities were included, in addition to criteria related to health impact. Figure 15.4 shows the outcome of this exercise, confirming the importance of *Taenia solium* at a global level.

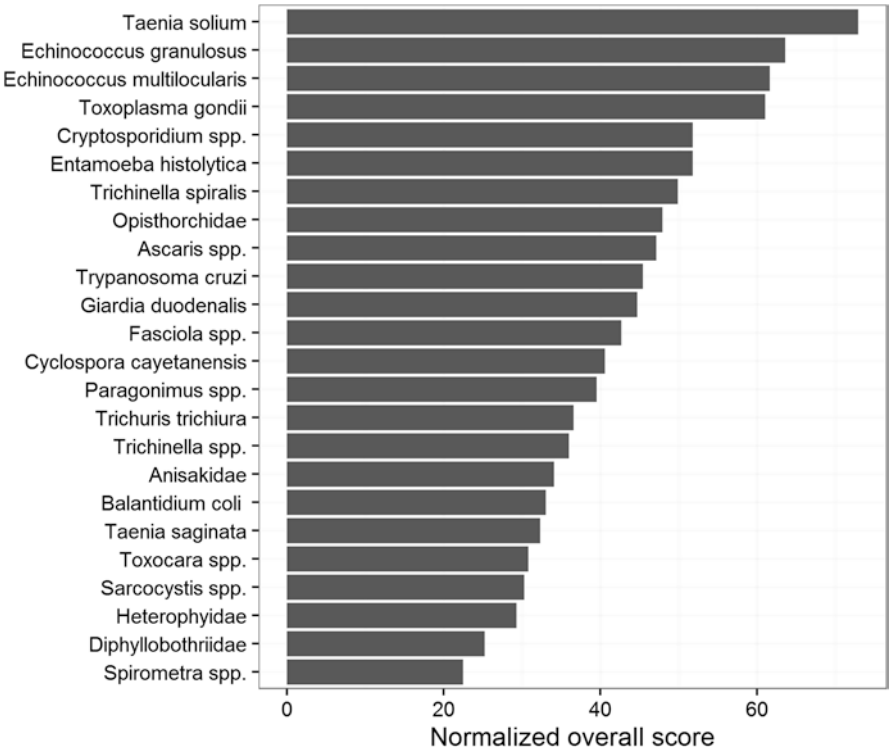

Fig. 15.4 Multi-criteria-based global ranking of foodborne parasites according to FAO/WHO (2014)

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