HAZARD-SPECIFIC METHODOLOGY

The following material is derived from, and in some parts repeated verbatim from, text in the suite of papers in which the FERG results have been published.[1] These primary outputs are listed below, and have been collated in a dedicated PLOS collection entitled "The World Health Organization Estimates of the Global Burden of Foodborne Diseases", which can be accessed at the website: http://collections.plos.org/ferg-2015. We acknowledge the PLOS for permission to incorporate this material into this report. In addition to the series of published papers, the estimates of foodborne disease burden have been made available as an on-line tool which will be accessible via the WHO FERG web page.[2]

Havelaar, A.H., Kirk, M.D., Torgerson, P.R., Gibb, H.J., Hald, T., Lake, R.J., Praet, N., Angulo, F.J., Bellinger, D.C., de Silva, N.R., Gargouri, N., Speybroeck, N., Cawthorne, A., Mathers, C., Stein, C., Devleesschauwer, B. on behalf of the World Health Organization Foodborne Disease Burden Epidemiology Reference Group. 2015. World Health Organization global estimates and regional comparisons of the burden of foodborne disease, 2010. PLOS Medicine, DOI: 10.1371/journal.pmed.1001923

Kirk, M.D., Pires, S.M., Black, R.E., Caipo, M., Crump, J.A., Devleesschauwer, B., Döpfer, D., Fazil, A., Fischer-Walker, C.L., Hald, T., Hall, A.J., Keddy, K.H., Lake, R., Lanata, C.F., Torgerson, P.R., Havelaar, A.H. & Angulo, F.J. 2015. World Health Organization estimates of the global and regional disease burden of 22 foodborne bacterial, protozoal and viral diseases, 2010: A data synthesis *PLOS Medicine,* DOI:10.1371/journal.pmed.1001921

Torgerson, P.R., Devleesschauwer, B., Praet, N., Speybroeck, N., Willingham, A.L., Kasuga, F., Rokni, M.B., Zhou, X.-N., Fèvre, E.M., Sripa, B., Furst, T., Budke, C.M., Carabin, H., Kirk, M.D., Angulo, F.J., Havelaar, A. & de Silva, N. 2015. World Health Organization estimates of the global and regional disease burden of 11 foodborne parasitic diseases, 2010: a data synthesis. *PLOS Medicine,* DOI:10.1371/journal pmed.1001920

Gibb, H., Devleesschauwer, B., Bellinger, D., Bolger, P.M., Zeilmaker, M., Barchowsky, A., Oberoi, S., Wu, F., Ezendam, J., Zang, J., Carrington, C., Cliff, J., Verger, P., Pitt, J., Adegoke, G., Afshari, R., Baines, J., Bokkers, B., Mengelers, M., van Loveren, H., Rainis, H., O'Leary, K. & Liu, Y. 2015. World Health Organization estimates of the global and regional disease burden of four foodborne chemicals and toxins, 2010: a data synthesis. *F1000 Research.*

Hald, T., Aspinall, W., Devleesschauwer, B., Cooke, R., Corrigan, T., Havelaar, A., Gibb, H., Torgerson, P., Kirk, M., Angulo, F.J., Lake, R., Speybroeck, N. & Hoffmann, S. 2015. 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.* in press.

Devleesschauwer, B., Haagsma, J.A., Bellinger, D., Cole, D., Döpfer, D., Fazil, A., Fèvre, E., Lake, R., Maertens de Noordhout, C., McDonald, S.A., Pires, S.M., Speybroeck, N., Thomas, K., Torgerson, P.R., Wu, F., Havelaar, A.H. & Praet, N. 2015. Methodological framework for World Health Organization estimates of the global burden of foodborne disease.

[1] All estimates of burden of foodborne disease were reviewed by relevant WHO focal points before submission. In particular, each paper was reviewed by the Mortality and Burden of Disease Unit, Health Statistics and Information Systems Department, Health System and Innovation Cluster (Coordinator: Dr Colin Mathers) and cleared as required through Food Safety and Zoonoses Department located in Health Security Cluster at WHO Headquarters.

[2] http://www.who.int/foodsafety/areas_work/foodborne-diseases/ferg/en/ accessed 3 November 2015

PLOS ONE, vol 10, iss 12 DOI: 10.1371/journal.pone.0142498

Lake, R., Devleesschauwer, B., Nasinyama, G., Havelaar, A.H., Kuchenmüller, T., Haagsma, J.A., Jensen, H., Jessani, N., Maertens de Noordhout, C., Angulo, F.J., Ehiri, J., Molla, L., Agaba, F., Aungkulanon, S., Kumagai, Y. & Speybroeck, N. 2015. National studies as a component of the World Health Organization initiative to estimate the global and regional burden of foodborne disease. *PLOS ONE*, vol 10, iss 12, DOI: 10.1371/journal.pone.0140319

4.1 Hazard Selection

At the first meeting after the establishment of FERG, each hazard-based TF compiled a comprehensive universal list of foodborne hazards that could be addressed (see Appendix 3). Pragmatic decisions were then made about specific hazards for further work, based on the knowledge of TF members and applying the following criteria:

- Availability of data to estimate incidence; and
- Likely magnitude of foodborne component of burden of disease.

Each of the three papers from the hazard-based TFs (EDTF, PDTF and CTTF) includes supplementary material discussing the sources and methodology for the parameters used to estimate: incidence, clinical outcomes, duration, DW, mortality, age and sex distribution. The full details have been combined in Appendix 4. The material below explains the rationale for the sources and methods.

Burden of foodborne disease estimates were prepared for the 40 foodborne hazards causing 41 diseases shown in Figure 2.

The following methodology section describes the inputs and processes used to generate DALY estimates. This material is broadly structured as follows:

- estimation of incidence (or population attributable fraction);
- health states and disability weights;
- attribution of foodborne transmission; and
- computation.

Figure 2. Hazards for which burden of foodborne disease estimates were prepared by FERG, grouped according to TF. Hazards in grey boxes were addressed by individual TFs but were not included in the global overview. Hazards in blue boxes are pending.

PDTF	CTTF	EDTF (HAZARDS CAUSING HEALTH EFFECTS OTHER THAN ENTERIC DISEASE)	EDTF (HAZARDS CAUSING ENTERIC DISEASE)
***Ascaris* spp.**	Aflatoxin	*Brucella spp.*	*Bacillus cereus*[1]
Echinococcus multilocularis	Arsenic	*Clostridium botulinum*[3]	*Campylobacter spp.*[2]
Echinococcus granulosus	Cadmium	*Hepatitis A* virus	*Cryptosporidium spp*
Clonorchis sinensis	Cassava cyanide	*Listeria spp.*	*Clostridium perfringens*[1]
***Fasciola* spp.**	Dioxin	*Mycobacterium bovis*	*Entamoeba histolytica*
Intestinal flukes[4]	Lead	*Salmonella enterica (invasive infections) non-typhoidal*	Enteropathogenic *E. coli* (EPEC)
***Opisthorchis* spp.**	Methyl mercury	*Salmonella enterica Paratyphi A*	Enterotoxigenic *E. coli* (ETEC)
***Paragonimus* spp.**	Peanut allergens[5]	*Salmonella enterica Typhi*	*Giardia* spp.
Taenia solium			Norovirus
Toxoplasma gondii[6]			*Salmonella enterica* (non-invasive infections) non-typhoidal
***Trichinella* spp.**			*Shigella* spp.
			Shiga toxin-producing *E. coli* (STEC)
			Staphylococcus aureus[1]
			Vibrio cholerae

Note that salmonellosis and invasive salmonellosis are counted as a single hazard causing two diseases.

Notes: (1) 61 EUR and other subregion A (low mortality) countries only. (2) Includes Guillain-Barré Syndrome cases and deaths. (3) 61 EUR and other subregion A (low mortality) countries only, excluding WPR countries. (4) Includes selected species of the families Echinostomatidae, Fasciolidae, Gymnophallidae, Heterophyidae, Nanophyetidae, Neodiplostomidae and Plagiorchiidae (depending on data availability). (5) Only the burden for AMR A, EUR A and WPR A was assessed. (6) Separate estimates for congenital and acquired toxoplasmosis.

4.2 Enteric Hazards

The overall aim of the EDTF was to provide estimates of disease incidence and mortality (by age, sex and country or region) for diarrhoeal and other illnesses due to bacteria and viruses, by all causes and by selected aetiological agents, and including sequelae. Despite its name, the EDTF was not exclusively concerned with hazards causing enteric disease.

The initial list of hazards considered by EDTF is given in Appendix 3. From this list, entero-aggerative *Escherichia coli*, *Vibrio parahaemolyticus*, *V. vulnificus* and *Yersinia* spp. were excluded on the basis that there were insufficient data for global estimation and they were infrequent causes of foodborne disease.

During the course of the project, it was identified that burden estimates for three parasitic hazards (*Giardia* spp., *Cryptosporidium* spp. and *Entamoeba histolytica*) should be included with the hazards addressed by EDTF, given that that the primary disease caused by these organisms was diarrhoea, and the approach taken to estimate the burden of these hazards was applicable.

As shown in Figure 2, there were 21 hazards causing 22 diseases for which final burden estimates were prepared by EDTF. Of these diseases, four are distinct manifestations of *Salmonella enterica*

infection: invasive infections due to *S. enterica* serotype Typhi (*S.* Typhi); invasive infections due to *S.* serotype Paratyphi A (*S.* Paratyphi A); invasive infections due to non-typhoidal *S. enterica* (iNTS); and diarrhoeal disease due to non-typhoidal *S. enterica*.

Diarrhoea is a dominant feature for 14 of these diseases – ten caused by bacteria, three by protozoa, and one by a virus. One or more extra-intestinal manifestations, including bacteraemia, hepatitis and meningitis, are the dominant feature for the other eight diseases – seven caused by bacteria and one caused by a virus.

4.2.1 Estimating cases, sequelae and deaths for diarrhoeal diseases

For diarrhoeal diseases caused by *Campylobacter* spp., *Cryptosporidium* spp., *Entamoeba histolytica*, ETEC, EPEC, *Giardia* spp., norovirus, non-typhoidal *Salmonella* spp. and *Shigella* spp., because national estimates of foodborne diseases were only available from a limited number of countries, two approaches were used depending on the level of development of the country. The approaches have been described by a key accompanying publication [40].

The first approach, based on national estimates of the incidence of foodborne diseases, was applied to the 61 countries in low-mortality (EUR and other subregion A) countries [41– 49]. For countries with national estimates of incidence and mortality, these data were used. The median and associated uncertainty intervals for diarrhoeal diseases for the subregion were used to estimate incidence and mortality of diarrhoeal diseases for other countries within these subregions without national data [40].

The second approach was applied to the remaining 133 countries worldwide. For this approach, the WHO Child Health Epidemiology Reference Group (CHERG) method was modified to estimate diarrhoeal incidence and mortality for all age groups [50]. First, the overall incidence of diarrhoea from all causes (i.e. the "envelope" of diarrhoeal incidence) was estimated for 2010 by combining estimates of diarrhoeal incidence for children <5 years of age and persons ≥5 years of age [51, 52]. The overall diarrhoeal mortality (i.e. the envelope for diarrhoeal deaths) derived by WHO for 2010 was used.[3]
An aetiological proportion for each disease by region was derived from systematic reviews of stool sample isolation or detection proportions from inpatient, outpatient and community-based studies of persons with diarrhoea. Following the CHERG standard approach, developed because there is limited information on pathogens among people who have died, it was assumed that the distribution of pathogens observed among inpatients hospitalized with severe diarrhoea represented the pathogen prevalence among diarrhoeal deaths [50]. To derive aetiological proportions for children <5 years of age, it was assumed that the distribution of pathogens in outpatient and community studies represented the pathogen prevalence among diarrhoeal episodes for those who did not die. The same assumption was made for persons ≥5 years of age but due to sparseness of data, inpatient studies were also included. For some pathogens it was assumed that different aetiological agents, such as *Shigella* spp., NTS and *Campylobacter* spp. had similar clinical profiles.

Initial estimates for the 61 countries in low-mortality (EUR and other subregion A) countries had been prepared using this second "CHERG approach". However, it was recognized that for

[3] http://www.who.int/gho/en/ Accessed 6 June 2014

these developed countries this would overestimate incidence of diseases, in comparison with published estimates from the national studies available.

Estimates for cholera were based on the incidence among populations at risk for cholera in endemic and non-endemic countries [53]. The case fatality ratio (CFR) for cholera was 1% in WPR subregion B; 1% in SEAR B (except 1.5% in Bangladesh); 1.3% in EMR B; 3% in SEAR D; 3.2% in EMR D; and 3.8% in AFR [53]. For all other countries, it was assumed cholera occurred only among international travellers and did not result in deaths. In this instance, the median incidence from non-endemic countries with available data for cholera was applied.

Shiga-toxin producing *E. coli* (STEC) infection incidence and mortality were based on a systematic review [54]. Sequelae, more common with O157 infections, were haemolytic uraemic syndrome (HUS) and end-stage renal disease (ESRD). Based on review, it was estimated 0.8% of O157 infections and 0.03% of infections caused by other serotypes result in HUS, and 3% of HUS cases result in ESRD. It was further estimated that the CFR for HUS was 3.7%; for ESRD the CFR was 20% in the 35 subregion A countries; and 100% in other countries.

For the incidence and mortality of foodborne intoxications caused by *Bacillus cereus*, *Clostridium perfringens* and *Staphylococcus aureus*, data from national studies conducted in low-mortality countries were used. The median incidence from national studies was applied to the 61 countries in EUR and other subregion A countries. The burden due to these three foodborne intoxications in high- and middle-mortality countries was not estimated due to the absence of data on diseases caused by these pathogens in these countries. The median CFR from national studies was 0.003% for *C. perfringens* and 0.0025% for *S. aureus*; there were no *B. cereus* deaths.

It was considered that 31% of Guillain-Barré Syndrome (GBS) cases globally were associated with antecedent *Campylobacter* infection and that the CFR for GBS was 4.1% [55, 56].

Assignment of aetiology of diarrhoeal diseases when using the CHERG approach for middle- and high mortality countries was refined by adding in an aetiological proportion for pathogens not associated with foodborne transmission (rotavirus, astrovirus, coronavirus) and for unspecified diarrhoeal agents (pathogens that are possibly foodborne but with insufficient data for estimation, and unknown agents not yet discovered).

In our study, norovirus resulted in the largest number of cases of foodborne diseases and overall burden, highlighting the global importance of this agent. However, the disease model we used in the 135 middle- and high-mortality counties included only norovirus infections that resulted in a diarrhoeal illness. If we also included estimates for norovirus infections that resulted in vomiting without diarrhoea, there would be an estimated additional 163 million norovirus cases in these countries [57].

4.2.2 Estimating cases and sequelae of, and deaths due to, extra-intestinal diseases

For diseases caused by hepatitis A virus, *Brucella* spp., *Listeria monocytogenes*, *Mycobacterium bovis*, iNTS, *S.* Paratyphi A and *S.* Typhi, a variety of approaches were used, depending on availability of data.

Institute of Health Metrics and Evaluation (IHME) Global Burden of Disease 2010

(GDB2010) data were used to estimate the burden of disease for typhoid, paratyphoid and hepatitis A [58]. IHME provided country-specific, age-standardized prevalence data for typhoid and paratyphoid fever. These data were converted to incidence by dividing by duration, and partitioned into typhoid and paratyphoid assuming a 1.0 to 0.23 ratio [59]. Country-specific hepatitis A mortality data, stratified by age and sex, were converted to incidence assuming a CFR of 0.2%.

Rates of iNTS are highly correlated with HIV prevalence and malaria risk [60]. To estimate iNTS incidence globally, age-specific estimates of incidence from a systematic review [60] were used to construct a random effect log linear model using covariates of country-specific HIV and malaria deaths, and the log of Gross Domestic Product. As data were sparse, incidence for all ages was predicted, which was converted to age-specific incidence based on age profiles for iNTS cases in low and high incidence settings [60]. From this, iNTS incidence was predicted among persons not infected with HIV [61, 62]. To estimate deaths, it was assumed that the CFR for iNTS in non-HIV infected individuals was a uniform distribution with a range 5- 20% in sub-region B-E countries and range 3.9- 6.6% in sub-region A countries [63].

Estimates for *M. bovis* infections were based on a systematic review where the proportion of human tuberculosis (TB) infections due to *M. bovis* ranged from 0.3% in AMR to 2.8% in AFR [64]. Fifty-one countries were identified that were free from *M. bovis* in cattle, based on European Union certification and the World Animal Health Information System (WAHIS) of World Organization for Animal Health.[4] All countries in a region except those free from *M. bovis* in cattle were assumed to have the same proportion of human TB infections due to *M. bovis*. To account for internationally acquired infections, all countries free of *M. bovis* in cattle were assigned the lowest observed proportion of human TB infections due to *M. bovis* (0.3%). To derive estimates of human *M. bovis* incidence, WHO country-specific human TB incidences were multiplied by the estimate of the proportion of human TB infections that were due to *M. bovis* [65]. To estimate mortality associated with *M. bovis* that accounted for HIV co-morbidity estimates were used of mortality due to human TB in HIV-negative persons (WHO data). Mortality data were adjusted by assuming that the CFR for *M. bovis* was 20% lower than human TB, as *M. bovis* infections are more likely to be extrapulmonary [66].

To estimate the incidence and mortality for brucellosis a systematic review was updated and included additional data on 32 countries that were considered *Brucella*-free in livestock (free of *B. abortus* in cattle and *B. melitensis* in sheep and goats) [67]. Incidence data were imputed to countries without estimates using a Bayesian log-normal random effects model, except for countries that were *Brucella*-free in livestock [68]. To account for internationally acquired infections, all countries that were *Brucella*-free in livestock were assigned the median incidence of human brucellosis reported from these countries. The CFR for brucellosis was 0.5%, and 40% of cases resulted in chronic infections, and 10% of cases in males resulted in orchitis [69].

The incidence and mortality for listeriosis were estimated using a systematic review that is described elsewhere [70]. In accordance with standard burden of disease practice, stillbirths were excluded

[4] OIE - www.oie.int/wahis

in our baseline burden estimates. The CFR was 14.9% for perinatal cases and 25.9% for other cases.

Incidence and mortality data for botulism were only available from countries in Europe and North America. The estimation was limited to the 55 countries in EUR and AMR subregion A, which was based on the median incidence derived from countries with national estimates of botulism. It was estimated that 35% of botulism cases were severe and that the CFR of severe botulism was 15%.

4.3 Parasitic Hazards

At the first formal meeting of FERG, the PDTF initially reviewed all parasitic diseases that could be potentially transmitted by food (Appendix 3) with 14 parasitic diseases selected as high priority. The selection criteria of these 14 diseases was based on: proportion of foodborne transmission; severity of illness and/or sequelae; frequency of illness and/or sequelae causes; global relevance; particular regional relevance; propensity to cause outbreaks; and availability of existing evidence to derive burden estimates (see meeting reports from FERG 1 and 2).

Three intestinal protozoa genera – *Cryptosporidium, Entamoeba* and *Giardia* – were considered a priority, as they were likely to result in a high disease burden, and the frequency of citations for these parasites had been markedly increasing between 1990 and 2008. For methodological reasons, the burden of the three priority intestinal protozoa that cause diarrhoeal disease was estimated by the EDTF as described above. *Toxoplasma gondii* was also considered to be of high priority because of the potential serious sequelae. *Cyclospora* was also initially considered, but a decision was made to target resources to the other intestinal protozoa, as citation frequency had remained constant over the same period.

Foodborne trematodes of high priority were *Fasciola* spp., *Clonorchis* spp., *Opisthorchis* spp., *Paragonimus* spp. and intestinal trematodes such as *Fasciolopsis buski, Heterophyes* spp. and *Metagonimus* spp. Three cestode species were considered important: *Echinococcus granulosus, E. multilocularis* and *Taenia solium*. The cestode *Taenia saginata* was considered likely to have a very low burden for human health because of the lack of serious sequelae resulting from intestinal taeniosis, and hence was excluded from the priority list. Foodborne Chagas disease was also considered for possible inclusion at the second FERG meeting, but resources were not available to commission work on the foodborne transmission of a primarily vector-borne disease. Finally the nematode species believed to have high impact were Anisakidae, *Ascaris* spp. and *Trichinella* spp. Disease caused by the Anisakidae was later considered to be an uncommon foodborne disease and was subsequently removed from the priority list.

The incidence of each of the parasitic diseases was estimated where possible. For cysticercosis, the burden was estimated from a proportion of the prevalent epilepsy cases, i.e. the number of actual cases of disease, as further detailed below. Those incident cases with sequelae (or diseased individuals) were assigned years of life lost (YLLs) if fatal, or years lived with disability (YLDs) with a DW that depended on the severity of the disease. For some diseases, such as toxoplasmosis, many of the incident cases do not have sequelae (i.e. they are sub clinical). Such cases were given a DW of zero.

Systematic reviews were undertaken to estimate the incidence, sequelae and

mortality due to these diseases [71- 77]. Where possible, public health records describing numbers of cases presenting for treatment were reviewed. These data were only available for some diseases in some countries. In others surveillance data were used (for example laboratory data on sero-conversion rates in the population).

For congenital toxoplasmosis (CT) a systematic search of nine major databases for published and unpublished sources was conducted, alongside direct contact with the authors of source materials. Searches were country specific. To be included, studies had to report on the incidence of CT, on positivity to *Toxoplasma*-specific IgM in infants and pregnant women (including sero-conversion results) or on positivity to *Toxoplasma*-specific IgG in the general population. Various modelling techniques were used, depending on the country-specific data available, to estimate the CT incidence and burden in each country. Reports of children born with CT, IgM serology of infants and pregnant women, and age-stratified sero-prevalence in women and the general population, combined with fertility rates of specific age groups, were used to directly estimate the incidence of CT, or the data was used to input into models that were able to generate CT incidences from IgM-sero-positive rates in children or pregnant women, or from the IgG-sero conversion rates in women, combined with age-specific fertility rates. These data were then synthesized into an estimate of the global incidence of CT and of the global burden of CT in disability-adjusted life years (DALYs). Further details of the methodology, inclusion criteria, PRISMA statement and the modelling techniques used are given in [76]. Data on sero-prevalence were also used to estimate the incidence of acquired toxoplasmosis. Thus changes in sero-prevalence between age of T and T+1 can be used to estimate incidence.

Incidence estimates and clinical sequelae, for diseases caused by foodborne trematodes, were mainly based on the results of two review articles [77, 78]. Incidence rates for countries without reported national prevalence were imputed, but only where there were reports of at least one autochthonous human infection, by using a hierarchical random-effects model and incidence information from other countries as input data [79]. In highly endemic zones, adult subjects either maintain the parasites acquired when young or can be newly infected as the consequence of inhabiting a zone of high infection risk. This suggests that, in those areas, the majority of infected adults should be chronically infected. However, acute lesions by repetitive infections are frequently superimposed on chronic disease [80]. Therefore, it is reasonable to assume that such overlapping series of repeat infections result in life-long sequelae. Thus the incidence of trematode infection was estimated from the numbers of new cases in each age cohort.

To estimate the incidence of alveolar echinococcosis (AE), due to infection with the larval stage of *Echinococcus multilocularis*, literature searches were undertaken in any relevant databases that could be accessed. These data sources were synthesized to obtain estimates of the incidences of AE in countries where *E. multilocularis* was known to be endemic. Further details of the strategy to obtain the data, together with the methodology to estimate incidences from the data, are described in the report from FERG 2. For cystic echinococcosis (CE), due to infection with the larval stage of *E. granulosus*, the results of a systematic review [73] and other databases were used.

T. solium neurocysticercosis (NCC) is known to cause epilepsy and other neurological sequelae [73]. A meta-analysis revealed that brain lesions due to NCC are present in approximately 29.0% (95% UI 22.9%- 35.5%) of people with epilepsy in populations living in *T. solium* endemic areas in settings with poor sanitation and pig management practices, and where pork is consumed [74]. Consequently, the incidence, prevalence, mortality and burden of disease due to epilepsy (including both idiopathic and secondary) used in the Global Burden of Disease Study 2010 (GBD2010) [58, 81- 83] were used to estimate the burden of epilepsy-associated NCC.

Once the population at risk was known, 29% of the burden of epilepsy from GBD2010 was applied to that population to estimate the burden of epilepsy attributable to NCC. Although NCC can show many other neurological and psychiatric symptoms [81], in the absence of available consistent data on these other sequelae, only the burden of NCC-associated epilepsy was estimated in this study.

In the case of NCC, prevalence-based YLDs were used. However, in the absence of evidence of strong temporal trends in incidence, this is a reasonable approximation for incidence-based YLDs.

Data on the global prevalence of human ascariosis, stratified by age, gender and country, were provided by the Institute for Health Metrics and Evaluation (IHME). Based on these data and using the life expectancy of the parasite (approximately 1 year), the equivalent incident cases were estimated from the prevalence data. The sequelae proposed in GBD2010 [82], were used in this study.

To assess the global incidence and clinical effects of human trichinellosis, outbreak reports were analysed. Searches of six international databases yielded 494 reports, of which 261 were selected for data extraction after applying strict relevance and reliability criteria. From 1986 to 2009, there were 65 818 cases reported from 41 countries, with 42 deaths. The apparent annual incidence of and mortality caused by trichinellosis was calculated by dividing the average number of cases and deaths in this 24-year period by the 1997 mid-year population. Due to the important variability in reporting of the disease, the apparent incidence and mortality rates per billion persons per year were adjusted to account for under-reporting of the cases due to under-ascertainment, medical misclassification, and/or absence of effective surveillance systems. The data analysis focused on incidence, age and sex of patients, major clinical aspects including sequelae, and meat sources of infection. Full details of the search criteria, data sources and analysis are described in [71]. The global burden of trichinellosis was subsequently estimated, which is described elsewhere [84], where full details of the methodology are given.

Of the 12 PDTF hazards (including congenital and acquired *Toxoplasma gondii* as separate entities), two hazards did not need imputation. For epilepsy due to *Taenia solium*, we applied the GBD2010 burden envelopes [81]. For trichinellosis, the regional estimates generated by Devleesschauwer *et al.* [84] were applied. For the 10 remaining hazards, the total number of countries with missing data ranged from 5 to 90 (out of 194 countries included). Among the 194 countries included, the number of hazards for which no data were available ranged from 0 to 6 (out of 10 hazards). For the five most populous countries in the world, the number of hazards with no data were 0 (China), 6 (India), 3 (United

States of America), 2 (Indonesia) and 3 (Brazil).

4.4 Chemicals and toxins

At its first meeting, the CTTF identified groups of chemicals and toxins that are of highest priority in estimating the burden of foodborne disease (Appendix 3). The hazards were ranked on: (1) the severity of potential health effects; (2) the prevalence of exposure; and (3) the availability of data to make burden estimates. After considerable discussion, the final list of chemicals and toxins for which the CTTF believed that burdens could be estimated were aflatoxin[5], cyanide in cassava, peanut allergen, dioxin and dioxin-like compounds[6], methylmercury, lead, arsenic and cadmium. Only the results for aflatoxin, cyanide in cassava, peanut allergen, and dioxin are presented here. The results for the metals will be provided in a subsequent publication.

For each of the four chemicals, a systematic literature review was conducted. It was concluded that burden estimates could be developed for: (1) cyanide in cassava, and associated *konzo* syndrome; (2) peanut (*Arachis hypogaea*) allergy; (3) aflatoxin and hepatocellular carcinoma (HCC); (4) dioxin and hypothyroidy; and (5) dioxin and decrease in sperm count.

4.4.1 Cyanide in cassava

Cassava is an important staple for over 800 million people in approximately 80 countries, mostly in sub-Saharan Africa but also in Asia, the Pacific, and South America [85]. Cassava tubers contain a varying quantity of cyanogenic glucosides, which protect the root against attack by animals and insects. Appropriate processing before consumption can reduce cyanogenic glucoside content of cassava. High dietary cyanide exposure occurs when high-cyanogenic cassava and insufficient processing combine, usually in a context of food shortage. Cyanide in cassava is associated with acute cyanide poisoning and several diseases, including *konzo* [86]. Worldwide reports exist of acute poisoning from cyanide in cassava [86], but the data are inadequate to make burden estimates. The data are sufficient, however, to make burden estimates of *konzo*. *Konzo* is an irreversible spastic paraparesis of sudden onset, associated with the consumption of bitter cassava [87, 88] and a low protein intake [89]. It is a disease of extreme poverty. *Konzo* mostly occurs in epidemics, but sporadic cases are also reported. The case definition includes the following criteria: (1) a visible, symmetrically spastic abnormality of gait while walking and/or running; (2) a history of abrupt onset (less than one week), followed by a non-progressive course in a formerly healthy person; and (3) bilaterally exaggerated knee and/or ankle jerks without signs of disease in the spine [89, 90].

Because *konzo* mostly affects remote rural areas where health infrastructure is poor or non-existent, many cases remain undiagnosed or unreported, so the true burden of disease remains unknown. No cases have been reported from urban areas. A total of 2376 *konzo* cases have been reported in 5 countries in Africa (Cameroon, Central African Republic, Democratic Republic of Congo (DRC), Mozambique, and United Republic of Tanzania) [86], corresponding to 149 cases per year for 122 million people. Dividing the average annual number of cases for each country by the corresponding country population produces an observed incidence ranging from 0.043 to 0.179 per 100 000. The

[5] The term, "aflatoxin," refers to all aflatoxins.

[6] The term, "dioxin," refers to dioxins and dioxin-like PCBs.