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Priority Setting for Foodborne and Zoonotic Pathogens

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Corresponding author:

Professor Arie Havelaar RIVM, PO Box 1 3720 BA Bilthoven the Netherlands

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Priority Setting for Foodborne and Zoonotic Pathogens

Michael Batz, Marie-Josée Mangen, Annemarie Käsbohrer, Tine Hald, J. Glenn Morris, Jr., Michael Taylor, and Arie Havelaar

A SUMMARY FOR AN INTERNATIONAL CONFERENCE ORGANIZED JOINTLY BY THE EU MED-VET-NET NETWORK OF EXCELLENCE AND THE US FOOD SAFETY RESEARCH CONSORTIUM 19-21 July 2006, Federal Institute for Risk Assessment, Berlin, Germany

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Introduction

There is nearly universal agreement that food safety priority setting decisions should be informed by scientific information and analysis, beginning with a data-driven approach to ranking the public health impact of specific foodborne hazards. Work is underway to establish protocols for how such food safety risk ranking should be done. Much of the focus is on development of an integrated framework for pathogen risk ranking to support priority setting decisions that combines epidemiological information on disease incidence, data on the attribution of these illnesses to foods, knowledge about the symptoms, medical treatments, and health outcomes of disease, and the economic and quality-of-life impacts of these health outcomes. A variety of methods and data sources have been developed by researchers in Europe, the United States, and elsewhere, towards such an integrated framework. To discuss the similarities and differences in these approaches, towards finding common agreement on principles and improving international collaboration, the E.U.'s MED-VET-NET* and the U.S.-based Food Safety Research Consortium (FSRC)† organized an international conference convened in Berlin, Germany, on 19-21 July, 2006. This report draws in part on the deliberations of the conference and discusses general principles, data needs, methodological issues and challenges, and future research needs pertinent to an integrated framework for priority setting for foodborne and zoonotic pathogens.

Human illness due to foodborne and zoonotic pathogens remains a persistent problem because of its tremendous complexity and dynamic nature. Complexities include a large number of unique microorganisms that cause a wide range of human health outcomes, a vast array of foods and animals that serve as vehicles for human exposure, and a wide range of causative and contributing factors that affect contamination, growth, persistence, and inactivation throughout the farm to fork food continuum.

It is in the context that decisions must be made on how to allocate resources and how to target interventions towards reducing the risk and public health impacts of foodborne disease. Quite

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^{*} MED-VET-NET is a European network of excellence, working for the prevention and control of zoonoses and food borne diseases. For more details see the website: www.medvetnet.org/cms/.

[†] The Food Safety Research Consortium is a multi-disciplinary collaboration of several institutes from the United States with the aim to improve public health. For more details see the website: www.rff.org/fsrc/.

simply, the opportunities to intervene are profuse, while the resources available are finite. The decision-making process necessarily weighs many factors, including social values, public and peer perceptions, politics, market forces, and others, but should be informed by objective, data-driven analysis that identifies which hazards cause the greatest impact on public health and which opportunities to intervene are most effective, and cost-effective, for reducing risk.

There is a need, therefore, to develop integrated approaches to risk-based food safety prioritization across a range of pathogens, foods, and public health impacts. It is important to distinguish between two contexts for food safety priority setting: the broad perspective or system-wide resource allocation that calls for the prioritization across a large number of pathogens and foods, and the targeted risk management perspective that calls for the prioritization of opportunities to reduce risks due to specific pathogens in specific foods. Put simply, this is the difference between identifying the worst problems and identifying the best solutions. For this paper, we are concerned with the former, which may be typified by exercises that rank the risks associated with different hazards. The latter requires different kinds of analysis that focus on assessing specific risk factors from the farm to the fork that may be addressed through interventions.

Notable attempts at priority setting of infectious disease have been performed in recent years. Canada ¹² and the UK ³⁴ have ranked communicable disease priorities based on expert consultation and scoring. The World Health Organization (WHO) has ranked illnesses using mortality, morbidity, DALYs (Disability Adjusted Life Years) and by human risk factors ⁵.

There have been several efforts to prioritize foodborne pathogens. Petersen et al. ⁶ ranked infectious agents transmissible to humans through consumption of undercooked beef based on numerical scores on potential hazard and exposure. Ross and Sumner ⁷⁸ developed and used a simple spreadsheet-based tool for semi-quantitative risk assessment to rank 10 seafood hazard/product combinations. U.S. federal agencies ranked 23 ready-to-eat foods for risk of foodborne *Listeria monocytogenes* based on results of quantitative microbiological risk assessments (QMRA). Ontario, Canada, has developed a method of systematically ranking food safety risks for resource allocation using a semi-quantitative approach based on expert scoring ⁹. The Food Safety Research Consortium (FSRC) has developed a quantitative risk ranking model that estimates health outcomes due to 28 pathogens and 13 food categories and ranks these food-pathogen combinations using five measures of annual public health impact, including number of illnesses, hospitalizations, and deaths as well as

in Quality Adjusted Life Years (QALYs) and economic valuation of illnesses ¹⁰. In the Netherlands, the National Institute for Public Health and Environment (RIVM) has performed analysis to prioritize community-acquired pathogenic micro-organisms. Nine pathogens have been included in this framework thus far, with more to follow ^{11 12}. Ranking criteria used are incidence numbers, Disability Adjusted Live Years (DALY) and cost-of-illness, for either all cases affected, or for a specified section in the gastroenteritis pyramid separately. Under development is the attribution of incidence and health valuation estimates to food categories.

Key Principles

Although there are different methodological approaches to risk-based priority setting of foodborne and zoonotic pathogens, there are some key principles upon which analyses should be based. Priority setting tools and approaches should be:

objective and based on quantitative estimates of public health impact – although semi-quantitative approaches that utilize expert scoring can be informative, it is preferable to utilize data-driven analytical approaches that minimize subjective values;

<u>practical</u>: the analysis needs to be applicable to real-life situations and take into account the needs of the decision-maker, limitations of data, and the costs of analysis;

grounded in a systems-understanding and based on the best science – within the bounds of practicality, the analysis should incorporate knowledge of how foodborne illness is caused and prevented, and incorporate the most recent data available;

<u>transparent and flexible</u> – within the bounds of practicality, the analysis should be transparent about assumptions, data sources, uncertainties, and limitations, and allow for the examination of these aspects of the analysis;

used to inform public policy but not to impede decision-making – public health and regulatory decisions must often occur despite incomplete information and uncertainties, and the desire for better analysis should not paralyze decision-making regarding immediate problems;

and <u>iterative</u> – the analysis should be repeated to re-evaluate priorities as new data and knowledge become available, particularly to reflect changes over time.

In addition to these principles, there are some concepts specific to comparisons between hazards, namely in risk ranking exercises, that should be followed.

First, risk categories should follow the guidelines put forth in Morgan et al. 13, which stipulates that risk categories for risk ranking should be: (1) logically consistent – exhaustive, mutually exclusive, and homogenous, (2) administratively compatible - compatible with organizational structures and legal mandates, numbered high enough for targeted response, and compatible with existing data, (3) equitable – balanced across interests of stakeholders, and (4) compatible with cognitive constraints and biases – aware of framing biases, simple enough to work with people's mental models, numbered low enough that the task is tractable, and free of the "lamp-post" effect caused by being overly selective at the start. These guidelines have a few implications for ranking zoonotic and foodborne pathogens, namely that the analysis should include a large number of pathogens and a broad array of pathways of exposure. For foodborne illnesses, when other potential sources of exposure such as water and direct contact with animals are excluded, it may be most natural to rank using pathogen-food pairs. Ranking pathogen-food pairs is useful because regulations and interventions are nearly always specific to a food and pathogen: i.e., control measures for Salmonella in chicken or preventing E. coli O157:H7 contamination of leafy greens. These guidelines also suggest that the food categories used should be comparable across pathogens – that is that it is inappropriate to compare the public health impacts of Salmonella in all poultry to the impacts of Campylobacter in broiler chickens only.

Second, to the extent possible, risk rankings should be methodologically consistent to ensure comparability between hazards. Otherwise, the ranking becomes more a function of the differences between assumptions and methods. For example, it would be problematic to compare risk assessment estimates of illness for one pathogen-food pair to estimates of illness for another pathogen-food pair based on extrapolations from outbreak data. Care must even be taken with estimates done at different times, as assumptions may vary between one analysis and another, and as the relative importance of sources is likely to vary over time as well.

Third, rankings should use integrated measures of disease burden that combine information on acute and chronic symptoms, different severities, and outcomes for pathogen-specific illnesses. Integrated measures are critical for ranking public health because they allow disparate diseases to be compared on the same comprehensive basis. Ranking pathogen-food pairs by estimated annual

fatalities, for example, ignores the impacts of chronic sequelae and acute morbidity. The three major approaches to integrated measures of burden are the use of HALYs (Health Adjusted Life Years), the monetary valuation of health outcomes as measured mostly through willingness-to-pay (WTP) approaches, and the economic cost-of-illness (COI). All three approaches are discussed in some length in later sections.

Incidence and Sequelae of Foodborne Infections

Pathogens transmitted via food cause gastrointestinal or non-gastrointestinal infection, resulting in significant morbidity and mortality worldwide ¹⁴⁻¹⁷. These pathogens may be 'known' bacteria, viruses, parasites or other micro-organisms, or may be 'unknown' or unidentified. These infections continue to have a major impact on the public health and economy of industrialized countries. While the majority of foodborne illnesses present with symptoms of gastroenteritis (GE), there are numerous foodborne pathogens that present with primarily non-enteric symptoms such as e.g. hepatitis, neurological syndromes, allergic, kidney damage, paralytic illness or death.

When assessing the public health impact of foodborne infections several issues have to be addressed:

- (a) how to estimate the incidence of disease (gastrointestinal and non-gastrointestinal infection; both may need different approaches and procedures for diagnosis)
- (b) how to identify and quantify the different outcomes,
- (c) how to quantify them in relation to the causative agent,
- (d) how to link 'foodborne exposure' to disease in case of long-term between infection and morbidity
- (e) how to estimate the proportion attributable to foodborne transmission
- (f) what is the impact of specific situations such as the usage of antimicrobials and the emergence of resistant bacteria,
- (g) what is the impact of the changing population and the increase of more susceptible groups such as the elderly and immunocompromised on these estimates.

Reported and estimated incidence

The most widely used public health indicator to quantify the impact of foodborne illness on a population is the estimation of the incidence of diseases associated with specific pathogens. Such

incidence estimates may result from studies that first target syndromes, such as e.g. gastroenteritis, followed by etiological studies on the agents involved, or may result from studies that first target a specific pathogen, followed by studies on associated syndromes.

Most often used as a basis for such estimates is the reported laboratory-confirmed incidence of specific pathogens or syndromes, which may be captured in a number of different surveillance systems, including outbreak surveillance, passive surveillance of notifiable diseases, and active surveillance and monitoring of laboratories. Outbreak surveillance may be based on national reporting from local or regional public health agencies or individual physicians, and often includes laboratory confirmation of etiology. Laboratory-based surveillance collects on a continuous basis, capturing information obtained for the treatment of individual patients. Many of these surveillance systems capture both enteric and non-enteric diseases due to specific pathogens.

Surveillance systems are often sustained on a permanent basis, which allows data to be analyzed for trends. Most of these types of surveillance system are passive-surveillance approaches based either on physician reporting of sporadic cases of notifiable diseases and the reporting of (foodborne) outbreaks. Passive surveillance systems rely on patients visiting physicians and those physicians identifying the pathogen through stool or blood tests. A Dutch study has shown that the test requests do not always comply with existing knowledge of the etiology of gastroenteritis ¹⁸. Further, in a passive surveillance system the tests used across public health laboratories may not be necessary standardized, as might be also the case for the reporting of laboratory-confirmed cases to the surveillance system. These problems might be largely overcome in a more advanced surveillance system such as e.g. the US FoodNet (Foodborne Diseases Active Surveillance Network), in which each sample is always tested for a clearly defined range of pathogens, using standardized tests and standardized reporting methods, and in which reporting is actively monitored. Active surveillance activities such as FoodNet may increase quality by limiting the set of pathogens or covering only a subset of geographic area.

For many syndromes associated with foodborne disease, such as e.g. gastroenteritis (GE), only a small proportion seeks medical care. Consequently the incidence of laboratory-confirmed cases associated with specific enteric and non-enteric pathogenic illness, whether collected in an active or passive surveillance system, represents only the tip of the iceberg of actual illness in the population ¹⁹

²⁰. There are numerous approaches to estimating the degree of under-ascertainment, or under-reporting, of diseases in the population by such surveillance systems.

One approach to estimate GE incidence in the population – and thus to get at the underascertainment of surveillance systems – are telephone surveys of physicians and of the general
population that might allow to estimate the proportion of cases unrecognized at each layer in the
surveillance pyramid, and correct for this. Such surveys are generally based on self-reported
syndromes that occurred in the past. It is also possible to perform serological testing on such selfreported cases to identify etiology, but precise knowledge of antibody decay profiles for enteric
pathogens is poor and so this type of follow-up is rare. Studies with self-reported syndromes,
however, are generally overestimated and do normally not include etiological information. Incidence
estimates for specific pathogens, therefore, are only possible by combining different source
information. But these types of surveys are far less time-consuming and far less expensive than e.g.
prospective conducted population cohort studies. However, potential biases, and difficulties to
determine the robustness of the pathogen-specific multipliers are the price to pay.

One application of surveys to account for under-reporting is presented by Mead et al. ¹⁵, which estimated the total number of cases, using information from active and passive surveillance systems, and adjusted for underreporting using multipliers from the literature. Many of the multipliers were based on FoodNet surveys of the population that asked how often they would visit physicians under differing severities of diarrhea, and similar surveys of physicians that asked how often when presented with patients with diarrhea they requested stool samples and how often they tested for specific pathogens. Specificity and sensitivity information on microbial tests were also used in these multipliers.

Detailed analysis of large outbreaks might be another source to determine pathogen-specific underreporting. It may be possible to estimate the relationship between the levels of a pathogen-specific GE reporting pyramid by examining how the cases entered the outbreak surveillance system (e.g. whether by hospitals, physicians, or directly from consumer complaints). Such information, in combination with data from laboratory-confirmed surveillance systems, might allow for an extrapolation of the number of cases in the general population. Outbreak situations might not be comparable to sporadic cases in the population, however. Differences in susceptibilities of subpopulations, in size of doses, or in other key areas can lead to differences in clinical symptoms, and therefore in likelihood of seeking medical care. Intensive press coverage during an outbreak may also lead to increased health care seeking behavior ²¹.

In addition to surveillance systems based on laboratory-confirmation of etiology, alternative approaches to estimating incidence may first start with estimating incidence of a syndrome, such as e.g. gastroenteritis, and subsequently follow up with studying etiology. One of these approaches is the telephone survey approach mentioned previously, but there are other examples. A prospective conducted community-cohort study combined with a GP-cohort study was used in the UK ²⁰ ²² and in the Netherlands ¹⁹ ²³ to estimate gastroenteritis incidence at the different layers of the surveillance pyramid. Conducting prospective studies, targeting at specific syndromes such as e.g. GE, followed by etiological studies and with a registration of outcomes and medical services used, are probably one of the most viable information source available, for incidence numbers, etiologies, multipliers and outcomes. Depending on the information collected such studies might also offer information on the resources used, both medical and non-medical for either all gastroenteritis cases ²⁴ ²⁵ or for some specific pathogen estimates ²⁴ ²⁶. However, such studies are very time-consuming and expensive, given that a large cohort has to be included in order to obtain a sufficient number of cases ²⁷.

For pathogens such as e.g. *Toxoplasma gondii*, serological markers might be used to estimate incidence numbers. Using either incidentally collected population samples (e.g. ²⁸), or routinely collected serology such as for example for *Toxoplamsa gondii* the pre-nuptial tests in France and Luxembourg (J. Mossong (Luxembourg), pers. communication, June 2006), the pre-natal tests from pregnant women ²⁹ or newborns ³⁰, country-specific antibody decay profiles might be estimated. Having a detailed knowledge of antibody decay profiles (e.g. ³¹), the so-obtained prevalence estimates of infection might be transformed into incidence estimates [‡].

Syndromes and outcomes

While the number of illnesses is a useful measure of the public health impact of enteric and nonenteric diseases, it does not capture the important information regarding the syndromes and outcomes of these illnesses. Not all illnesses are the same, not even for those primarily presenting with gastroenteritis. Illnesses due to different pathogens vary in terms of clinical symptoms and

[‡] This issue is the subject of the MED-VET-NET workpackage 32. For more details see: www.medvetnet.org/cms/templates/doc.php?id=63&searchstring=workpackage%2032.

medical treatment. As severity of illness also varies by pathogen, so too do rates of hospitalization and mortality. Even for pathogens presenting with very similar initial symptoms, subsequent outcomes may differ markedly.

In addition to acute gastroenteritis, infection with enteric pathogens can result in sequelae that may develop as complications of acute symptoms or that can present themselves following recovery. The most well known sequelae are hemolytic uremic syndrome, Guillan-Barré Syndrome, reactive arthritis, post-infectious Irritable Bowel Syndrome, sepsis and others. The main challenge to associating these syndromes with foodborne infection is that these sequelae occur infrequently; disease onset is often only after a few weeks of recovery from acute gastroenteritis, so a link to specific pathogens cannot be accurately identified; and furthermore these sequelae can be caused by several microbiological agents, both enteric and other pathogens. The different sources of information described hereafter are suitable for both, enteric and non-enteric pathogens, but also for the analysis of sequelae. However, a longer follow-up period than usually applied, and eventually larger sample sizes might be required, depending on the illness and the expected risk to develop the syndrome under study.

For information of the upper layer, regular hospital discharge diagnosis, mortality registration and other similar sources might provide useful for incidence estimates, outcomes and resources used, at least for certain syndromes. For gastroenteritis, however, those sources are often too general, as the ICD codes (ICD = International Classification of Diseases) of interest, include not only gastroenteritis. Furthermore, the microbiological agent causing GE is seldom registered ²⁷. The records are further influenced by the purpose of reporting, i.e. the amount of money received depending on the code used. Prospective hospital studies, followed by etiological studies, would provide accurate information about hospitalization, potential complications, including premature death, and the resources used. But as already mentioned earlier, any type of prospective study conducted, independent of the population studied, is generally very time-consuming and expensive, and therefore rather an exception.

A novel epidemiological method to estimate illness outcomes was applied in Denmark for Salmonella, Campylobacter, *Yersinia enterocolitica*, *Escherichia coli* and Shigella ^{32 33}. Based on a personal identification number attributed to each citizen residing in Denmark and used in public health registries, it was possible for the authors to link different registries. Registry-based, matched cohort

studies were run, where for every laboratory-confirmed patient, a reference group of ten persons was selected. In addition, data on all hospital admissions and discharge diagnoses within the time span of up to ten years prior to entry in the study to one year after, were used to control for pre-existing illness (comorbidity) and to determine the excess mortality associated with infections ³², as well as to determine the risk of hospitalization associated with severe gastroenteritis, complications or long-term sequelae ³³. These registry-based cohort-studies target first a specific pathogen, followed by studies on associated syndromes, whereas in most of the other data sources discussed so far, incidence estimates first target syndromes, such as e.g. gastroenteritis, followed by etiological studies on the agents involved. The only exception is serological marker surveillance data.

Case-control studies may also be used to estimate outcomes of disease for specific pathogens. Casecontrol studies are performed for several purposes, such as determining risk factors or attributing illnesses to foods, and are usually conducted for laboratory-confirmed cases, but can be applied to most of the approaches discussed above. Case-control studies are conducted either as a prospective or a retrospective study, mostly relying on self-reporting. Self-reported symptoms should ideally be confirmed by medical examinations. For example, Hannu et al. 34 conducted a prospective conducted case-control study to determine the risk of developing reactive arthritis (ReA) after a laboratory-confirmed Campylobacter infection. About 38% of the contacted patients reported recent joint or other muscular-skeletal symptoms, however, after medical examinations and tests, the authors estimated that only 7% had developed ReA and 1% reactive tendonitis, enthesopathy or bursitis. The same authors found a comparable occurrence of reactive arthritis following Shigella infection (7%) in another population based study 35. These authors reported both, incidence numbers and the use of medical services, similar to Locht et al. 36, however, the latter was a retrospective study without medical examinations. Studies of selected sequelae have been run by FoodNet between 1998 – 2000. Persons with a laboratory confirmed infection caused by a bacterial pathogen, i.e. Campylobacter, Salmonella, Shigella, Yersinia, E.coli O157, Vibrio or Cryptosporidium were asked about any health problems before their enteric infection and any health problems developed since their infection. Several sequelae were reported, but infrequently ³⁷.

Complicating factors

Quantifying the public health impact of foodborne illness is complicated, perhaps increasingly so, by a number of additional factors that may need to be considered, such as sensitive or susceptible populations, distinct pathogen subtypes, antimicrobial resistance, demographic and behavioral changes, and changes in the food system.

There are pathogens that result only in mild or subclinical infections in the general population, but can cause severe symptoms and premature death in specific subpopulations, such as the immunocompromised or pregnant women. For example, Cryptosporidium has been known to develop severe illness in HIV patients, resulting in premature death, a very unlikely outcome for otherwise healthy individuals. In such situations, extrapolations from a surveillance system or from other studies towards the whole population may require corrections for such affected subpopulations. In addition, pathogens may affect certain age groups, such as children or the elderly. Although integrated measures of disease burden allow for illnesses in different groups to be compared, the decision-maker or society may be particularly sensitive to certain groups, such as pregnant women, infants, or young children.

Furthermore, pathogen subtypes can differ in terms of virulence or severity levels in the population, but detailed information is not often known and may not be adequately captured in surveillance systems, making it difficult to extrapolate from such data to the full population. Similarly, changes in the antimicrobial resistance of pathogens may affect the severity of clinical symptoms as well as the effectiveness of medical treatment, and also may not be adequately captured in disease surveillance systems. Depending on the scope of differences in strains, whether in virulence or in anti-microbial resistance, separate or specialized data collections may be necessary to fully characterize the impacts of certain pathogens on the population.

These factors are further complicated by a food system that is dynamic. Changes in food production processes and technologies, global supply chains that are constantly shifting, population demographic trends, and shifting consumption patterns mean that the supply and demand for food are never static, and foodborne risks may change from year to year.

Attributing Illnesses to Foods

To make informed prioritization decisions about foodborne illnesses, it is important to identify and quantify the vectors of disease, which means identifying the pathogens that cause illnesses and the vehicles of exposure to these pathogens (e.g. foods, water, pets, etc). For broad prioritization decisions, this means determining the proportion of total illnesses that can be attributable to food,

identifying which specific foods are responsible for which illnesses ("food attribution"), and quantifying the relative contribution of these foods to the total disease burden associated with foodborne pathogens.

The attribution of illnesses to foods is a growing area of research that incorporates an increasing number of analytic approaches and data sources. A detailed discussion of food attribution issues, including the advantages, applications, and limitations of many of these approaches, may be found in Batz et al. ³⁸. It is important to note that the utility of different approaches varies by the question driving the attribution. For example, a cost-benefit analysis of a specific intervention in a specific food requires good estimates of the number of illnesses "saved" due to the intervention, but broad priority setting calls for understanding the relative importance of numerous exposure routes.

Methodological Issues

One critical issue is the importance of the "point of attribution" – that is, the location in the production to consumption continuum that is addressed by a specific approach. Attribution focused at the point of production identifies the animal reservoirs or sources of on-farm microbiological contamination prior or during harvest, whereas attribution at the point of consumption or exposure identifies dishes as they are eaten, after preparation and cooking. Different types of data and different analyses may point to different points of attribution, and even the same type of data may point to multiple points of attribution. For example, one outbreak may be traced back to the farm while another may be traced to cross-contamination in the kitchen from another food product. Aggregated outbreak data (across geography and over time) that simply identifies food vehicles may include both of these kinds of attribution points, so care must be taken in the analysis and in the reporting of results.

The food system is dynamic, which means that attribution estimates are snapshots in time that quickly become out of date. It may not be clear how to interpret apparent trends moving forward or how to aggregate data over time. Changes in the durable immunity of the population or of the antimicrobial resistance of pathogens affect attribution, as do changes in consumption patterns and changes in contamination due to regulatory change or implementation of interventions.

The issue of "food categorization", while seemingly straightforward, is important, and often a difficult issue to resolve. Due to the complexity of the food system, there are many ways in which

foods can be grouped into bins, with important implications for interpretation of results. Categorization also impacts the ability to compare the results of different methods. Without standardized categories, there is a reduced potential to validate or "ground-truth" results, or to combine data in a meaningful way. It may be difficult to compare the differences between countries or over time if the categories don't line up.

Data on contamination may come at any point in the farm to fork spectrum, and the grouping of foods may depend on where in this spectrum attribution is being made. Foods as eaten are complex dishes made up of numerous ingredients, so categories used to analyze data on foods as eaten should reflect this, whereas on-farm or reservoir attribution targets specific species of plant or animal. Even so, there are multiple ways to categorize foods. For example, one might organize products into fruits and vegetables to reflect common sense groupings, or into row crops and tree crops to reflect differences in production (and likely risk factors) that apply to fruits and vegetables alike. Similarly, there may be fuzzy boundaries between foods: for example, should bean sprouts be binned with legumes and beans to reflect their species, or with salad greens to reflect how they are most often consumed? Additional categorization factors may be location of production (domestic, imported), production type (organic, conventional), level of processing (raw, fresh-cut, canned, etc), location of preparation (home, restaurant, etc), or degree of preparation (raw, cooked, reheated).

Difficulties arise when there may be categorical schemes that have overlapping purposes. For example, one scheme may group all pork products together and then differentiate between cuts and processed deli meats, while another scheme may first separate out cuts and deli meats and then differentiate between animal species. While these two schemes might be able to be broken down into the same ultimate categories (e.g. cuts/pork and deli/pork), the aggregated numbers cannot be compared. Given these kinds of complexities, it may be difficult to develop a standardized scheme, but a nested or tiered approach might resolve most of the major issues and allow for more generalized studies.

Attribution Approaches

There are a number of approaches that have been used for the attribution of illnesses to pathogenfood pairs, including analysis of outbreak data, retrospective case-control studies, natural experiments, microbial fingerprinting, risk and exposure assessments, and expert elicitation. Microbial fingerprinting approaches to attribution are based on the premise that animal species carry unique host-specific populations of microorganisms, which can be identified through microbial subtyping and used to link isolates drawn from infected persons to specific animals. The term "microbial fingerprinting" is most often used in relation to genetic subtyping approaches such as pulsed field gel electrophoresis (PFGE) and phenotyping approaches such as the use of serotypes, but the concept can be pursued using a number of other methods, including the use of antimicrobial resistance patterns, chemical markers, biomarkers, bacteriophages, and viral markers ³⁹. Using different analytical methods, Denmark and the Netherlands have been employing fingerprinting to successfully attribute salmonellosis cases to animal species for some time, and the U.S. has recently begun investigating this approach 40-42. Subtyping approaches have shown promise for some other pathogens, such as E. coli O157:H7 and Yersinia enterocolotica biotype 4 serotype O:3, but have not been as yet successful for other pathogens, such as Campylobacter. The fingerprinting approach is data intensive, as it requires advanced laboratory analytics be performed on isolates from infected humans as well as on a substantial number of representative isolates drawn from multiple reservoirs/sources. While microbial fingerprinting identifies the animal reservoir ultimately "responsible" for illness, some illnesses may not be caused by consumption of that species but due to cross-contamination during processing or preparation or to environmental exposure. This is particularly important for attribution of disease to produce. For example, the subtype of E. coli O157:H7 identified in the 2006 U.S. spinach outbreak matched subtypes taken from nearby cattle and feral pigs, but whether or not diseases should be attributed to spinach or animal species depends on the context. People got sick from eating spinach, to be sure, but the policy response to these illnesses may ultimately extend beyond the borders of spinach production.

Epidemiological approaches to attribution rely on public health surveillance and work "backwards" from incidence of disease to determine the food vehicles. Compilations of the results of outbreak investigations are useful because they provide a direct measure of attribution, and the data may be analyzed to suggest, for example, what percentage of illnesses due to a specific pathogen were due to a specific food vehicle. There are numerous examples of outbreak attribution (e.g. ^{10 43-45}). The key advantage of analyzing outbreaks is that common data are available for many pathogens by year at the national level, and therefore comparable data exists for a wide swath of illnesses. The major disadvantages of using outbreaks are misclassification bias because outbreaks are uncharacteristic of sporadic cases, investigation bias due to variation in investigations by geography, time, and outbreak

characteristics such as size, duration, setting, causative organism, and others, and detection bias due to the fact that there are systematic reasons why certain vehicles may be identified over others ⁴⁶. It is important to recognize that outbreaks provide point of consumption information that often includes illness due to improper handling and preparation practices, including cross-contamination, and care must be taken not to make inferences about foods further back in the production chain.

The other major epidemiological approach used is case-control studies, in which patient-cases for specific pathogens and asymptomatic controls are interviewed about recent food consumption and other behaviors, and the data statistically analyzed to determine the population attributable fraction (PAR) due to each identified exposure route ⁴⁷. Case-control studies have been performed in numerous countries, including the U.S., Denmark, and the Netherlands ⁴⁸⁻⁵². Two advantages of case-control studies are that they are usually based on sporadic cases and controls are matched demographically to cases, so they are more representative of overall causes of illness than outbreak data, though unlike outbreak data, food vehicles are not laboratory-confirmed. As case-patients are usually selected from laboratory surveillance (and not surveillance of the general population), they are biased by severity and medical treatment. Interview-based data are affected by recall bias and by selection bias of what risk factors are in the questionnaire. Due to long exposure windows and durable immunity, it is difficult to identify PAR for common (non-emerging) illnesses and those associated with commonly consumed foods. Commonly consumed foods also require large study sizes. Despite these factors that might affect the accuracy of individual PAR, case-control studies can identify the rank-order of risk factors.

Natural experiments are "silver lining" events in which changes in consumption patterns due to food shortages, mass recalls, regulatory changes, or other causes, can be quantifiably associated with changes in illness surveillance (e.g. ⁵³)^{54 55}. Although useful, such occurrences are rare and provide limited snapshot information about a single exposure route.

While epidemiologic approaches work "backwards" from illness to attribute to foods, risk assessments based on predictive microbiology work "forwards" from pathogen contamination of foods to estimate illnesses due to that pathogen-food pair. Risk or exposure assessments are generally performed for a specific pathogen and exposure pathway such as consumption of a particular food product, so in order to compare the relative importance of numerous foods or pathways, a suite of assessments must be performed. Quantitative microbial risk assessments rely on

many different kinds of data including survey data on contamination of foods and water, models of pathogen growth, persistence, and inactivation in relevant conditions, data on these conditions and risk factors between contamination and human exposure, food consumption data, and dose-response models, among others. Large uncertainties in the exposure assessment modeling can make comparisons between pathways difficult, and uncertainties in dose-response functions hinder the ability to compare across pathogens, but there are also significant - though less often explicitly quantified - uncertainties in other attribution approaches. Due to their high resource requirements, risk assessments hold more promise for targeted prioritization questions than for priority setting across a large number of pathogens and foods. In the U.S., risk assessments for *Listeria monocytogenes* in 23 ready-to-eat foods were used to understand relative risks between these foods ⁵⁶, while in the Netherlands, exposure assessments were performed to compare 20 food and water consumption pathways and 11 environmental contact pathways for *Campylobacter* spp. ⁵⁷.

When scientific data are lacking, uncertain, or conflicting, as is often the case with food attribution, expert judgment gathered through structured elicitation protocols may be used to fill data gaps or combine information in a coherent and meaningful way. Expert judgment derived through formal protocols are increasingly used and recommended for risk assessment and cost-benefit analysis ^{58 59}. Elicitations might ask experts to provide relative attribution percentages across a set of foods, as was done in the FSRC study ^{10 60}, or to provide weights for combining multiple estimates, or simply to provide the rank-order of a set of exposure pathways. Expert judgment is not "data driven" in the traditional sense, though elicitations should attempt to maximize the extent to which experts can reflect on available data. Likewise, as with any survey or interview approach to data collection, there are many biases that can affect results, from subtleties of wording to choice of experts to systematic biases in existing data or knowledge, so effort must be made in the elicitation protocol to minimize these biases. Lastly, critical to success of expert approaches is that they are transparent.

In comparing data from attribution studies, and in developing new approaches, it is important to evaluate the characteristics of these efforts. Namely, Batz et al. ³⁸ suggests to consider "scientific accuracy and uncertainty, quality and breadth of data, computational consistency, practical feasibility, cost of implementation, flexibility and scalability, utility for targeting interventions, and congruency with other relevant data sources," and to "balance such factors as scientific accuracy and practical feasibility to produce attribution data that will be both useful and affordable."

There may be yet new methods to attribution that have not yet been explored. It is likely that the approaches that are likely to yield the best attribution numbers are those that explicitly link data from surveillance of human illnesses with data on pathogenic contamination of foods. It is also likely that to improve the results of attribution approaches, we need to improve the data upon which they are based. This might entail increases in the microbial testing of foods, animals, and non-food exposure routes and greater inclusion of attribution purposes in large active surveillance efforts. Regardless, differences in data are likely to persist. Therefore, through expert or analytical approaches, we must improve the ability to combine information, particularly data from epidemiological investigations with predictions from risk assessments.

Integrated Measures of Disease Burden

Combining the impact of the number of cases with the cases' severities, and eventually with the associated economic impact, is in economic literature frequently referred to as the burden of disease ^{5,61-64}. Estimates of the incidence of disease are useful but limited measures of the impact of foodborne illness because they are incomplete and because they cannot be easily compared to one another or to other public health concerns. Simple incidence numbers do not capture the full impacts of illnesses – i.e. the number of illnesses, hospitalizations, and deaths do not capture important aspects of symptom severities, treatments, or chronic sequelae. Moreover, without integrated measures, different diseases cannot be compared to one another, or to other public health concerns. For example, if a decision maker wished to compare the impacts of foodborne infections to the impacts of other infectious diseases, such as hepatitis B, or other public health problems, such as car accidents, using the number of cases would be inadequate. For such comparisons, it is preferable to use an integrated measure of disease burden that combines the incidence estimates with information on severities, outcomes, treatments, and chronic sequelae. Furthermore, with full economic accounting, in which monetary values are applied to all direct and indirect effects and costs, including intangible costs such as suffering and premature death, it is possible to compare health projects to projects in other sectors 63.65, such as for example the building of a bridge.

A burden of disease analysis is generally composed of two steps ⁶⁶. The first step is a thorough evaluation of the epidemiologic data describing the illness, whereas the second step consists of an analysis of the health effects in terms of their impact on the ill and society. There are three prominent approaches to valuing impacts of disease: Health-Adjusted Life Years (HALYs), Cost-of-

Illness (COI) and Willingness-To-Pay (WTP). There are examples of all three methods published in the food-safety literature and related areas (e.g. ⁶⁷⁻⁷²). There are significant differences between the three main methods and their underlying assumptions, and further distinctions within each method.

Health indices to value human health

Health-adjusted Life Years (HALYs) are non-monetary health indices that are often used in cost-effectiveness studies. In the HALY approach, an individual's health is evaluated on a severity scale (usually from 0 to 1) and this health score is multiplied by the duration of that health state. HALYs are generally additive, which means that one can add up HALYs for an individual over time, and one can add up HALYs across individuals. Thus, for a particular pathogen over a full year, one can add up the HALYs lost through premature mortality, through mild, moderate, and severe health states, and through chronic sequelae of illness.

Referring to a specific HALY, known as a Quality Adjusted Life Year, or QALY, Krupnick et al. ⁶⁴ describes the situation thus:

'A basic assumption is that the QALY values are additive, so that a treatment eliminating extreme pain for one year for two individuals (2 x 0.5) is equivalent to a treatment that adds one healthy year of life. Life years are treated equally for all individuals, implying that a single healthy year is weighted the same regardless of age or income.'

HALYs are used in economic cost-effectiveness analyses (also sometimes referred in the literature as cost-utility analysis or weighted cost-effectiveness analysis). Quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) are probably the two most prominent examples of HALYs found in the literature.

In the QALY approach, the quality adjustment is based on a set of values or weights called utilities, one for each possible health state, that reflect the relative desirability of the health state. In the QALY approach is death weighted with 0 and perfect or excellent health is equal to 1. Every health state in between is given a quality weight ranking between zero and one ^{62 64}. The quality-adjusted life expectancy in the population is measured without and with the condition. The attributed quality weight is comprised of different attributes or dimensions components describing the health state. Different instruments exist to attribute a specific quality weight to a certain health state, resulting in

slightly different quality weights, if used simultaneously (for examples see Gold et al. ⁷³ and Drummond et al. ⁶²).

The DALY approach was first developed by the World Health Organization's Global Burden of Disease (GBD) program to compare the impact of specific diseases in different countries ⁷⁴. The DALY method presumes perfect health for the entire life span, and therefore measures the loss due to ill health. Death, - that is the worst possible health state -, is then also assigned a disability weight of 1 and 0 represents the best health state. The burden of disease in a population is measured by taking the prevalence or the incidence multiplied by the corresponding DALY loss. In the original GBD project age-weighting was applied to reflect the fact that individuals have different roles and changing levels of dependency and productivity with age ^{74 75}. Age-weighting, however is highly debated ⁷⁶. Studies that do not apply age-weighting argument, that their disease burden estimate reflects solely the intangible costs of suffering, bad health and premature death. Disability weights are generally estimated in panel elicitation. There exist several preference measurement methods, giving different results if used simultaneously, but they are highly correlated.

Although, DALYs and QALYs, as two examples of HALYs, were developed for distinct purposes (for an overview see for example Gold et al.⁷³), both methods are suitable as a measure of disease burden for analysis in food safety, having both strengths and weaknesses. Furthermore, HALYs are a suitable tool allowing the comparison of food safety projects with other health projects.

Attributing monetary values to human health

A significant disadvantage of the HALY approach is that a comparison with non-health projects is not possible. Further, one cannot compare the economic costs of an intervention to the potential benefits. To do so, non-monetary effects such as e.g. health effects require the assigning of a monetary value. But what is the monetary value of an improvement in life quality or length of life? According to the literature there are two general approaches to the monetary valuation of health outcomes. These are: (1) the human capital approach, which measures a person's renewed or increased production in the market-place; and (2) the willingness-to-pay (WTP) approach, which measures what individuals would be willing to pay to obtain health improvements, or less commonly, what individuals would be willing to accept (WTA) for a health decline 62 64. The WTP and WTA approaches are not only suitable to value mortality but are also used to value other non-monetary goods.

With the human capital approach, the benefit of a health programme is measured by how it helps the patient return to, or increase, their productive output. The human capital approach is generally restricted to the impacts on labour productivity ⁶². One issue however, is what "shadow-price" to consider for non-market resources such as for example a homemaker? Opportunity costs of time or a replacement cost approach are the two methods usually used to value this time ⁶². However, this production-based method for valuing health is not a real measure of individual or social welfare, since it makes no attempt to include intangible, but real, losses in well-being.

In contrast, the WTP approach is based on the trade-offs that individuals must make between health and other goods, and are therefore consistent with the theoretical foundation of welfare economics ⁶². The most well-known WTP measure is the VSL or value-of-statistical-life, a practical estimation that is not intended to place a monetary value on life itself, but which refers to what an average individual in a population is willing to pay to avoid the risk of premature death. WTP can be measured by evaluating the trade-offs people actually make (revealed preferences) or by presenting people with hypothetical choices (stated preferences) 62 64. In revealed preference studies, the relationship, between particular health risks associated with a hazardous job and wage rates that individuals require to accept the job, is evaluated. This approach is theoretical based on 'individual preferences regarding the value of increased (decreased) health risk, such as injury at work, as a trade-off against increased (decreased) income, which represents all other goods and services the person might consume' 62. In the stated preferences of WTP respondents are hypothetical scenarios measuring a) preferences for reductions in the risk of death; and b) measuring preferences for reductions in morbidity ⁶⁴. Various research methods have been developed to elicit from individuals their monetary valuation of health benefit, whereby hypothetical questions may be asked in a closed or open-ended manner. Stated preference and revealed preference approaches each have their advantages and limitations. Stated preference studies can be designed for a specific question, but rely on a hypothetical construct that may not reflect the choices people make in the real world, once acting as "consumers". Likewise, revealed preference studies depend on real-world situations and data that are often hard to come by and difficult to collect, which may not reflect the specific value sought, and which may include confounding factors that make it difficult to draw the revealed preference from the data. WTP is a successful research area and is developing rapidly. However, willingness to pay is a function of ability to pay and therefore results may be a reflection of wealth as much as a valuation of benefit. The values reported in the literature vary quite widely between

countries, and even within countries. For example, Viscusi and Aldy ⁷⁷ summarize the results from 30 labour market studies and find that the estimate of the value of a statistical life varies between \$0.7 million to \$20.8 million per statistical life in 2000 US dollars. A complicating factor in economic evaluation of food safety problems is that severe cases and fatalities are more likely to occur in immunocompromised individuals, such as children and the elderly. But the WTP of elderly people and of children (or rather of the parents of children) may differ from the WTP of an average population ⁷⁸.

Adverse health and economic flow of associated monetary costs

A third approach is the cost-of-illness (COI) method. The COI approach traces the economic flow associated with an adverse health outcome by identification and quantification of the associated monetary costs. Unlike WTP estimates, COI estimates do not measure "pain and suffering" as COI includes only measurable costs to the economy, such as medical costs and productivity losses (lost days of work).

A cost-of-illness study is therefore a cost study whereby the mostly negative effects of illnesses (costs) are described and quantified. There are four categories of costs that might be included: 1) Direct Healthcare Costs (DHC), 2) Indirect Healthcare Costs (IHC), 3) Direct Non-Healthcare Costs (DNHC), and 4) Indirect Non-Health Care Costs (INHC). DHC includes the valuation for medical services such as doctor consultations, hospitalization, drugs and other medical services used by the patients themselves as a consequence of the illness acquired. If insured, these costs are largely covered by health insurances. IHC would comprise the future savings in health care costs in the life years lost due to premature death, a highly controversial category (see e.g. Brouwer et al. ⁷⁹) usually omitted in cost studies. Travel costs of patients, informal care (= care delivered by family members and other non-medical persons) and other co-payments paid by patients are some examples for DNHC. These are costs that are directly related to the illness but occur outside the health care sector. INHC are all type of costs indirectly linked to the illness and occurring in other sectors than the health care sector. Productivity losses due to work absence of patients and/or third persons taking care of sick people are one of the major costs in this category. Examples of other costs include costs for special education or re-education after having been disabled due to illness.

Apart for the evaluation of productivity losses (INHC), few differences exist for valuing costs. However, differences in national health care systems (e.g. going directly to specialist, or only after being transferred by a general practioner) complicate the transferability of data from one country to another. In the case of productivity losses, there are two valid methods, the human capital approach and the friction cost approach. The human capital approach, which is based on neoclassical labour theory, estimates the value of *potential* lost production (or the potential lost income) as a consequence of disease of an individual. In the case of permanent disability or premature death at a specific age the total productivity value (or income) from that age until the age of retirement is counted as productivity losses. The human capital approach is in some studies also used as a proxy to value human health, as was highlighted in the previous section ^{62 64 80}.

According to the developers of the friction cost approach, however, the assumption of flexibility in prices which in turn results in markets clearing - one of the main assumption of neoclassical labour theory - is in many parts of the world no longer realistic ⁸¹. According to Koopmanschap et al ⁸², the real production losses for modern society are smaller. 'The friction cost approach aims then also to adjust the human capital estimates of productivity costs for the compensations that are likely to occur as a result of a labour market' ⁸¹. The friction cost method considers only production losses for the period needed to replace a sick, invalid or dead worker including a period of adaptation, the 'friction period' ⁸³. The length of the friction period depends on the situation of the labour market. A high unemployment rate generally allows fast replacement, whereas a low unemployment rate results in a longer average time for replacement. The friction cost method places a zero value on a person outside the labour market, such as children 15 and younger and retirees 65 and older. The human capital approach results in much higher cost estimates than the friction cost approach ⁸², especially when there are large numbers of deaths or disabled cases.

Comparing Integrated Measures of Disease Burden

To compare the three approaches, we used the five criteria presented by Alan Krupnick at the workshop. These five criteria are: 1) meaningful with respect to priority setting; 2) understandable to public and policy makers; 3) flexible with respect to aggregation over all types of effects; 4) comprehensive across realm of health states; 5) believable, as shown through validity tests.

With respect to meaningfulness, the HALY approach is built on assumption that a life-year is the appropriate metric. HALYs may or may not be trade-off based. A strong point of the HALY approach is that utilities and disability weights are not income-constrained. The WTP is built on the concept of consumer sovereignty and individual welfare. WTP can be based on individual

preferences towards group preferences. Although WTP is theoretically the golden standard, the trade-off value estimates are strongly income-constrained. The COI does not represent preferences, but is built on the concept of economic output. The COI is, when using the human capital approach, implicitly trade-off based and income constrained, conditions that might not hold when using the friction cost approach.

With respect to understandability, monetary values are implicitly understandable to people in terms of their daily lives. WTP is widely used in environmental risk assessments, but the methodologies for computation are complex and their use remains controversial, particularly in analyses with valuation of mortality. The COI method is not controversial, and most people understand and accept how it is computed. HALYs, a health metric, is widely used and well accepted method in medical decision making (choosing between alternative treatments, primarily), though controversial in other settings such as policy-making. The concept of applying index scores to health states is understandable to most people.

WTP is probably the most flexible method as in principle it can be applied to any type of effect, both health-related and non-health related effects. WTP can be used in cost-benefit analysis allowing a comparison not only of food-safety and health-related projects, but also of any other project. HALYs apply to all health effects and can be used in cost-effectiveness analysis. A comparison of projects is limited to health-related projects only. COI applies to all expenditure-based health and health-related effects. If not used as a method to value human health but rather to measure the economic flow associated with an adverse health outcome, the COI method might be combined with the HALY approach or the WTP approach.

The WTP covers in theory, if corrected for direct health care costs, nearly everything and would therefore be the most comprehensive method to apply. However, developing WTP measures is far more labour-intensive than developing HALYs because the latter approach provides weights for many different health states or domains in a given survey, while WTP studies yield values for at most a few health endpoints at a time. Therefore in practice most WTP studies do show many holes. Whereas the HALY approach mostly covers everything in its domain, and existing holes in practice are mostly relatively easily filled. However, this approach misses all non-health effects and health-related monetary costs. The COI method can be as complete as one wants within its domain, but this method misses all type of intangible costs such as pain and suffering.

Extensive internal and external validity testing is applied for the WTP method. For HALYs the focus of testing is on the validity of indices and on the validity of weights. Weights are sensitive to duration of effect, but also the method applied to estimate them. The underlying assumptions made in COI studies normally extensively documented, however often ad hoc choices cannot be excluded from this type of study.

The final conclusion is that there is no clear winner between HALY, WTP, and COI. All three have some pros and cons. WTP is conceptually the method most in line with economic theory, but it is controversial (low income people, misperception) and not comprehensive. And although HALY is accepted in the medical profession and simple to understand, there are many problematic underlying assumptions. The COI has the broadest coverage, but is not a welfare measure. The COI approach however, provides an *accounting* of the money spent, which is useful information to economists and policymakers. Therefore a combination of the COI methodology with either WTP or HALYs, both useful tools to measure health effects (mortality and morbidity), would provide an added value above any of the three methods alone. HALY and COI results in cost-effectiveness analysis (in the literature also sometimes referred as cost-utility analysis), limited to comparisons between other health-related projects. WTP and COI could be used in cost-benefit analysis, which has the advantage that a comparison between health and non-health projects is possible, e.g. reducing Salmonella versus building a new bridge.

A last point to remember is that all three methods, independent how complete they are, cover only a part of the national and international economic impacts. In order to decipher the full economic impact of illness and premature death, additional studies would be necessary. COI might then indicate the direction and magnitude of the economic flows resulting from health shocks to the economy ⁸⁰, if combined with e.g. a general equilibrium analysis the redistribution of economic activities in other sectors might be evaluated, which would be a first step in deciphering the full economic impact of illness and premature death.

Data Integration

Just as there is no single approach for estimating incidence, attributing illnesses to foods, or valuing the economic or quality-of-life impacts of illness, there is no single approach for combining the information into an integrated framework. Two examples of prioritization efforts – those initiated

for the Netherlands by RIVM and for the U.S. by the FSRC – illustrate two similar, yet distinct, applications of data integration.

For the Netherlands, an incidence-approach is used to estimate the disease burden, expressed in DALYs, and the associated cost-of-illness for the acute illness and sequelae for various community-acquired pathogens. Incidence estimates in the general population and at GP-level are mainly based on two prospective conducted studies, one a community-cohort study ¹⁹, and the other one a GP-cohort study ²³. Hospitalization rates for the various pathogens under study are either based on laboratory-confirmed surveillance data and various Dutch case-control studies, or are subtracted from the Dutch hospitalization database. Fatality rates are based on the published literature, as data on reported incidence of fatal cases is rather scarce. For estimates of sequelae and symptom duration, Dutch studies are used where available and international studies are used otherwise. Where possible, information on resources used and their required quantities are based on Dutch studies. If international literature has to be consulted, specificity of the Dutch health care system and the Dutch cost prices are used. Direct-health care costs, direct non-health care costs and indirect non-health care costs (mainly productivity losses whereby using the friction approach) are estimated from a social perspective.

The integrated results can be ranked by incidence numbers, Disability Adjusted Live Years (DALY) or cost-of-illness, for either all cases affected, or for a specified section in the gastroenteritis pyramid separately. The attendant uncertainty with the single results is also presented. Under development is the attribution of incidence and health valuation estimates, by percentage, to food categories.

For the U.S., the FSRC's Foodborne Illness Risk Ranking Model (FIRRM) combines incidence data, attribution information, and valuation of illnesses in monetary terms and in Quality Adjusted Life Years (QALYs) to enable ranking of pathogen-food combinations by their overall impact on public health. The annual number of cases, hospitalizations, and deaths due to 28 pathogens are estimated based on illness surveillance data and information on under-reporting from published literature. Laboratory-confirmed FoodNet surveillance data are used for 10 pathogens, passive surveillance of notifiable disease reporting are used for another 8 pathogens, outbreak data are used for 3 pathogens, and community studies and published literature are used for the remaining pathogens. Reported incidence is multiplied by under-ascertainment factors based on studies of population under-reporting, physician under-reporting, and test specificity and sensitivity. Hospitalization and

fatality rates are based on these same surveillance systems and the published literature. Health outcome trees divide total cases into branches (with associated likelihoods) for each pathway of health states; for example, total cases may be divided into those who require hospitalization, those who see a physician, and those who do not seek medical care, while hospitalized cases may subsequently recover completely, require long-term medical care for chronic symptoms, or die due to their symptoms. Each state (or branch) in each tree is valued in monetary terms and given a QALY health score. Willingness-to-pay estimates based on published literature are used to value mortality, while morbidity is valued using cost-of-illness approaches that consider medical costs and productivity losses. In FIRRM, COI values are not intended to estimate costs to the economy, but rather are used as a proxy for WTP values, as WTP estimates are sparsely available for non-mortality health states.

Attribution of illnesses (and associated health outcomes) to foods is performed in FIRRM based on two sources of data: outbreak surveillance and an expert elicitation study performed specifically for the model. For each pathogen, the proportion of outbreak cases in each of 11 major food categories (and 46 sub-categories) determines the percentage of illnesses to attribute to each category. In the expert study, participants were asked to attribute illnesses by percentage to the same major food categories, as well as prompted for uncertainty information. The user can choose either the outbreak data or expert data for rankings. Rankings are produced for pathogen-food combinations, pathogens, and foods by annual number of cases, hospitalizations, and deaths, as well as by monetary value and by QALY loss. The model is designed as an analytical tool, and allows for changes of assumptions and data sets. FIRRM also incorporates probabilistic uncertainty distributions for many input and output variables.

Discussion and conclusions

There are several approaches for estimating incidence, attributing illness to foods, valuing the economic or quality-of-life impacts of illness, and combining the information into an integrated objective data-driven framework. In an ideal world the different approaches would come up with the same general result. But, things are in reality much more complicated. The main difficulties exists in how data from different approaches can be compared, and whether certain methods can be standardized and generally applied. Therefore, cross-validation for all levels, from incidence

estimates through data integration, is important to fully understand the comparability of results from study to study, country to country and year to year.

It is important to recognize that the analysis in itself is not the end of the story. The data-driven analysis is but part of a decision-making process that includes many additional factors. To properly and fully convey the results to the decision-maker – and to the public – effort must be put into risk communication activities throughout the process. Likewise, there is a need to reconcile the possible difference between analytical estimates of the most important risks or hazards and the perceptions of the public.

An important aspect of the presentation of analytical results is the treatment of uncertainty. Any analysis is going to have uncertainties; the broad models and analyses used to prioritize foodborne illnesses and zoonoses are no different. Indeed, their scope is that of the full system, and the uncertainties are likely to be quite large. There are significant uncertainties in the estimates of incidence of disease, in the health outcomes of these illnesses, in the attribution of these illnesses to food vehicles, in estimates of QALY or DALY loss, and in health valuation and economic components. In addition to measurement uncertainties, there is temporal and geographic variability, heterogeneity in the population, and model uncertainties due to lack of information forcing the analyst to make assumptions and choices in the analysis.

It is widely acknowledged that uncertainties should be presented to decision-makers to provide them with a full understanding of the analysis, so as to avoid over-confidence in uncertain results. However, decision-making under uncertainty is an ongoing area of research. Non-technical readers and users may have difficulty with quantitative approaches, and even graphical approaches require some familiarity to be comprehended. Probabilistic measures of uncertainty, including variance, skewness, and kurtosis, as well as the distributions themselves, may not be understood. As such, there is no consensus as to the ideal way to present uncertainties. In general, point estimates should be avoided whenever possible; ranges or confidence intervals should be used in their place. Likewise, presentation of estimates should follow standard procedures for significant digits.

Even when uncertainties are presented, and risks fully communicated to the decision maker, the analysis is only one component, albeit a key component, in the ultimate decision. Additional factors play an important role, when taking a decision in the real world, including social values, public and

peer opinions and perceptions of risk, economic aspects, available resources, equity, and politics. Objective and data-driven analysis can help provide a scientific answer to the question "which problem is most important?" but these other factors may provide conflicting advice to the decision maker.

One factor that explicitly and directly affects the analysis is the perception of risk. According to Jensen et al. ⁸⁴, the lay perspective is primarily personal, whereas experts have a more impartial point of view of risks to society. Therefore, risks as estimated by the analysis may differ markedly from what the public, or even 'experts' believe to be the most important hazards. These perceptions are important because public agencies serve not only to minimize the public health burden of foodborne illness, but also to promote confidence in the food supply. Public agencies serve at the will of the people, and so public perceptions are important to consider in any decision framework.

There may be ways to integrate public perceptions of risk and social values more explicitly into priority setting analyses, and a few attempts in this direction in related fields can be found in the literature ^{85 86}. Social scientific research, using surveys or other tools, might be employed to rank risks according to public perception, and these data might be compared to the results of the data-driven analysis. The decision maker could use both sets of information to make resource allocation or priority setting decisions, and the analysis might suggest which pathogens are seen by consumers as having more or less impact than the data. It has to be noted, however, that public perception is only a snapshot, new events occur and public perception might change ⁸⁵. Alternatively, democratic deliberation may be used to bridge the gap between expert and lay perceptions or preferences about risk.

Research Needs

While the aforementioned methods for estimating incidence, accounting for severities and outcomes, attributing illnesses to foods, and computing integrated measures of disease burden are advanced and mature, there are substantive and pervasive gaps in data and knowledge throughout many of these steps. Many points were made during presentations and discussions at the conference identifying research needs. While the previous sections of this paper highlighted many of the limitations of various aspects of the analytical framework for priority setting and associated research needs, we find it useful to summarize the most urgent and important points here.

The surveillance of foodborne illnesses has advanced significantly in recent years, though improvements in these systems are still necessary. The etiology remains unknown for a large portion of cases of gastroenteritis likely associated with food consumption; this calls for improvements in detection methods, particularly for viruses, and for increased numbers of pathogens included in standard etiological tests. Likewise, increased subtyping and antimicrobial testing of pathogens may provide important information on the virulence of specific strains, and may be critical to establishing certain subtypes with particular species for attribution purposes. Improved reporting methods and rates would also increase the utility of these systems for estimating incidence. In particular, there is a need to better quantify the degree of under-ascertainment of surveillance systems at various levels of the reporting pyramid, including outbreaks and laboratory-confirmed cases. Improving the knowledge of antibody decay profiles for pathogens might be helpful in obtaining incidence for the whole population, as well as sub-populations. For priority setting purposes, the differences in under-reporting rates between pathogens may be critical, as current estimates for under-reporting range from 2 to 40 for common pathogens, and may be even higher for rarer or emerging pathogens.

There is also a need to better understand the symptoms, severities, and sequelae associated with different pathogens, as well as the likelihoods of these different outcomes. In particular, greater attention should be focused towards the chronic sequelae that may result from enteric infections from different pathogens. Irritable bowel syndrome, reactive arthritis, and Gullain-Barre syndrome have been associated with specific foodborne infections, but the mechanisms for causation are not fully known, and the rates of such sequelae are quite uncertain. It is possible that a significant portion of such chronic diseases in populations may be associated with foodborne infections, which only increases the importance and public health impact of these pathogens. Knowledge of antibody decay profiles for enteric pathogens might help to link these sequelae with enteric pathogens. Longer and more intense follow-up studies, combined with medical examinations, retrospective and prospective cohort studies, and case-control studies may help to obtain better estimates for such outcomes.

Collecting more economic information in addition to epidemiological data in future studies would help not only to improve estimates of incidence and outcomes, but also help to better quantify disease burden estimates and other economic impacts of the illness. Improved economic estimates may be useful for priority setting purposes, as well as for further cost-benefit studies on interventions aimed at specific pathogens. In addition, willingness-to-pay measures currently exist

for relatively few health states, namely mortality and some severe sequelae. WTP studies for mild and moderate health states are necessary to better understand how individuals value their ability to avoid these outcomes, so that integrated monetary valuation estimates are more accurate.

While these improvements to estimating incidence and quantifying health outcomes need further development, the area of greatest need in the priority setting framework is the attribution of illnesses to foods. Our ability to associate portions of population disease to specific pathogen-food combinations is impacted greatly by a dearth of information on sporadic cases of illness; while outbreak investigations attempt to identify a food vehicle, laboratory confirmation is rarely done in sporadic cases. For some pathogens, novel techniques such as the use of sub-typing to identify animal reservoirs, as has been done for Salmonella, may prove useful for estimating systematic attribution to food sources. This data-intensive approach has not been used as effectively for other pathogens, however. The direct linking of food isolates and human isolates on a system-wide scale is a good goal, but a distant one. Rather, in the short term, the array of methodological approaches that may be utilized for attribution should be considered an advantage, and rather than try to figure out which one is best, we should move towards trying to combine or integrate these attribution approaches. For example, for a particular pathogen-food pair, estimates of sporadic illness based on a case-control study might be added to estimates of outbreak cases based on past outbreak data. CDC is currently developing just such an approach, as discussed during this conference by Angulo ⁸⁷. By combining outbreak data and case-control studies and comparing to exposure assessments or risk assessments, it may be possible to bound estimates.

Approaches to integrating the various components of the framework may be improved. For example, the incorporation of lay or public perceptions of risk into the framework may be of some benefit. Other criteria, such as impacts to specific subpopulations, might also be brought into the framework.

There is a particular need to focus greater attention on the treatment of uncertainty in such priority setting efforts. Uncertainties in one part of an analysis may be characteristically distinct from those in other parts of the analysis, and thus might be treated differently; for example, self-expressed expert confidence levels used in attribution estimates might be best modeled differently than differences in the quality of disease surveillance between two regions. Eventually, however, these estimates must be combined into measures of uncertainties in overall results. This is complicated by

the likelihood of correlations between uncertainties. For example, the under-reporting multiplier for Salmonella is uncertain but is likely highly correlated with the multiplier for Campylobacter, since acute symptoms are so similar (though there are important differences in etiological testing). Thus, while the estimate of the number of cases of Salmonella and Campylobacter may have very wide confidence intervals, the relative difference between the two pathogens may be much less uncertain.

These complicated aspects of results play into the need for research into improved methods for communicating risk and presenting uncertainty to decision-makers and the public. Similarly, there is a need to put greater emphasis on cross-validation of different approaches. Validating results and understanding limitations and advantages impact the ability to compare results from study to study, year to year, and from country to country.

Conclusion

To make better food safety decisions informed by science and analysis, there is a need for an integrated framework to support priority setting decisions that combines epidemiological information on disease incidence, data on the attribution of these illnesses to foods, knowledge about the symptoms, medical treatments, and health outcomes of disease, and the economic and quality-of-life impacts of these health outcomes. There are alternative methodologies to each of these components of the model, though the overall approach retains some consistent principles and design features. There are important data gaps and uncertainties in many aspects of the integrated framework, and the need for further research to inform these types of analysis. Although an integrated analytical framework for priority setting is only a part of the whole decision-making process, we believe that such an objective and data-driven approach forms a basis for effective and efficient decisions on the control, prevention and surveillance of foodborne pathogenic microorganisms.

Acknowlegments

We would like to thank all participants of the conference, and in particular the presenters. We have the presenters to thank for much of the content that informs this report, as can be seen by glancing at the agenda in Appendix A. Furthermore, we have all of the participants listed in Appendix B to thank for the engaging discussions at the conference that were central to its success. We would also like to thank all those on the advisory committee (listed on the cover page of this report), who provided direction and assistance to the planning committee. In particular, we would like to thank Diane Newell and Bernd Appel, without whose strong support and dedicated guidance this conference would likely never have been held, let alone such a success.

We would further like to thank Elke Stellbrink and Jeannet Kemmeren for their contribution when preparing this conference, Heidi Spitznagel for her contribution during the writing of the report, and the Bundesinstitut für Risikobewertung (BfR) for hosting.

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Appendix A: Conference Programme

19-21 July 2006 Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment) Diedersdorfer Weg 1, D – 12277, Berlin, Germany

Wednesday, 19 July 2006

Session 1: Overview of priority setting approaches

Chairs: *Bernd Appel and Annemarie Käsbohrer* (Federal Institute for Risk Assessment, Berlin, Germany)

Opening address

Andreas Hensel (Federal Institute for Risk Assessment, Berlin, Germany)

Food Safety Priority Setting: Why and How?

Michael R. Taylor (University of Maryland, Baltimore MD, USA)

Management of the EU Food Safety System for Foodborne Zoonotic Agents and Its Needs for Priority Setting

Kris De Smet (European Commission DG Sanco, Brussels, Belgium)

How Does the US Food Safety System Work and What Information Do Risk Managers Need? *Robert L. Buchanan* (US Food and Drug Administration, CollegePark MD, USA)

Lay and Expert Perceptions of Zoonotic Risks: Understanding Conflicting Perspectives in the Light of Moral Theory

Karsten Klint Jensen (Danish Centre for Bioethics and Risk Assessment, Frederiksberg, Denmark)

Session 2: Incidence and outcomes of gastro-enteritis

Chair: J. Glenn Morris, Jr. (University of Maryland School of Medicine, Baltimore, MD, USA)

U.S. and WHO approaches to estimating the incidence and etiologies of gastro-enteritis *Elaine Scallan* (Centers for Disease Control and Prevention, Atlanta GA, USA)

EU approaches to estimating the incidence and etiologies of gastro-enteritis Sarah O'Brien and Goutam K. Adak (Health Protection Agency, London, UK)

Sequelae of gastroenteritis

Duc J. Vugia (California Department of Health Services, Richmond, USA)

Health impact of zoonotic *Salmonella* and other foodborne bacterial gastrointestinal infections. Register based studies.

Morten Helms (Statens Serum Institut, Copenhagen, Denmark)

Session 3: Incidence and outcomes of other non-enteric foodborne diseases

Chair: Klaus Stark (Robert Koch Institut, Berlin, Germany)

Incidence and outcomes of listeriosis

Kåre Mølbak (Statens Serum Institut, Copenhagen, Denmark)

Incidence and outcomes of toxoplasmosis

Ruth Gilbert (Institute of Child Health, London, UK)

Session 4: Attribution I – Getting started

Chair: *Arie H. Havelaar* (National Institute for Public Health and the Environment, Bilthoven, the Netherlands)

Summary of the work package 28 kick-off meeting

Tine Hald (Danish Institute for Food and Veterinary Research, Søborg, Denmark)

Reflections on the role of "source attribution" in risk analysis

Fred Angulo (Centers for Disease Control and Prevention, Atlanta GA, USA)

An Overview of Food Attribution Methodologies

Michael Batz (University of Maryland School of Medicine, Baltimore, MD, USA)

Campylobacter source attribution by exposure assessment

Eric Evers (National Institute for Public Health and the Environment, Bilthoven, the Netherlands)

Expert Opinion As A Method For Estimating Attribution Of Foodborne Infection Sources *Rob Lake* (Institute of Environmental Science and Research, Christchurch, New Zealand)

Thursday, 20 July 2006

Session 5: Attribution 2 – Epidemiological approaches

Chair: *Tine Hald* (Danish Institute for Food and Veterinary Research, Søborg, Denmark)

Analytical epidemiological studies

Fred Angulo (Centers for Disease Control and Prevention, Atlanta GA, USA)

US outbreak data

John Painter (Centers for Disease Control and Prevention, Atlanta GA, USA)

Using outbreak data for foodborne disease attribution: the U.K. experience *Sarah O'Brien* (University of Manchester, Salford, UK)

Session 6: Attribution 3 – Sub-typing approaches

Chair: Fred Angulo (Centers for Disease Control and Prevention, Atlanta GA, USA)

Source attribution using phenotypic subtyping of Salmonella

Tine Hald (Danish Institute for Food and Veterinary Research, Søborg, Denmark)

Microbial subtyping – genotyping

Peter Gerner-Smidt (Centers for Disease Control and Prevention, Atlanta GA, USA)

Interventions and attribution: The Iceland Campylobacter experience

Ruff Lowman (Canadian Food Inspection Agency, Ottawa, Canada)

Session 7: Integrated disease burden and economic indicators

Chair: Michael Batz (University of Maryland School of Medicine, Baltimore, MD, USA)

Health-adjusted Life Years (HALYs) to Measure Disease Burden

Dennis Fryback (University of Wisconsin-Madison, Madison, WI, USA)

Illness and related costs

Marie-Josée J. Mangen (National Institute for Public Health and the Environment, Bilthoven, the Netherlands)

Valuing Food Safety for Prioritization: WTP and Synthesis

Alan Krupnick (Resources for the Future, Washington DC, USA)

Session 8: Data integration

Chair: Robert L. Buchanan (US Food and Drug Administration, College Park, MD, USA)

FIRRM: The FSRC Foodborne Illness Risk Ranking Model

J. Glenn Morris, Jr. (University of Maryland School of Medicine, Baltimore, MD; USA)

Priority Setting of Foodborne and Zoonotic Pathogens – the Dutch experience

Arie H. Havelaar (National Institute for Public Health and the Environment, Bilthoven, the Netherlands)

Challenges and Opportunities in Risk Ranking of Microbial and Chemical Hazards in Food: an IFT Panel Experience

Greg Paoli (Decisionanalysis Risk Consultants, Ottawa, Canada)

Session 9: Emerging infections

Chair: Diane Newell (Veterinary Laboratories Agency, New Haw, UK)

Emerging enterohaemorrhagic E. coli (EHEC)

Lothar Beutin (Federal Institute for Risk Assessment, Berlin, Germany)

Mathematical models of the population dynamics of food-borne and zoonotic pathogens *Gary Smith* (University of Pennsylvania, Philadelphia, PA, USA)

Needs for emergency response

Peter Braam (World Health Organization, Geneva, Switzerland)

Friday, 21 July 2006

Session 10: Interactive session on research and data needs

Chair: *Arie H. Havelaar* (National Institute for Public Health and the Environment, Bilthoven, the Netherlands)

Conference report on research and data needs

Michael Batz (University of Maryland School of Medicine, Baltimore, MD, USA) and Annemarie Käsbohrer (Federal Institute for Risk Assessment, Berlin, Germany)

Panelists:

Goutam K. Adak (Health Protection Agency, London, UK)

Tine Hald (Danish Institute for Food and Veterinary Research, Soberg, Denmark)

Alan Krupnick (Resources for the Future, Washington DC, USA)

J. Glenn Morris (University of Maryland School of Medicine, Baltimore, MD, USA)

Session 11: Interactive session on international collaboration

Chair: Michael R. Taylor (University of Maryland School of Medicine, Baltimore, MD, USA)

Panelists:

Peter Braam (World Health Organization, Geneva, Switzerland)

Elaine Scallan (Centers for Disease Control and Prevention, Atlanta GA, USA)

Robert L. Buchanan (US Food and Drug Administration, College Park, MD, USA)

Diane Newell (Veterinary Laboratories Agency, New Haw, UK)

Jean-Charles Cavitte (European Commission, Brussels, Belgium)

Appendix B: Conference Participants

Jacques Acar

O.I.E.

Paris, France

jfacar7@wanadoo.fr

Katharina Alpers

Robert Koch-Institut

Berlin, Germany

AlpersK@rki.de

Yvonne Andersson

Swedish Institute for Infectious Disease Control

Solna, Sweden

yvonne.andersson@smi.ki.se

Frederick Angulo

CDC (Centers for Disease Control & Prevention)

Atlanta GA, USA

FANGULO@CDC.GOV

Bernd Appel

BfR (Bundesinstitut für Risikobewertung)

Berlin, Germany

bernd.appel@bfr.bund.de

Michael Batz

Resources for the Future

Washington DC, USA

mbatz@rff.org

Teresa Belcher

Society for Applied Microbiology

Bedford, Great Britain

teresa@sfam.org.uk

Lothar Beutin

BfR (Bundesinstitut für Risikobewertung)

Berlin, Germany

lothar.beutin@bfr.bund.de

Caroline Blobel

Bezirksamt Spandau von Berlin Abt. Soziales und

Gesundheit, Veterinär- und Lebensmittelaufsicht

Berlin, Germany

c.blobel@ba-spandau.verwalt-berlin.de

Sofia Boqvist

National Veterinary Institute

Uppsala, Sweden

Sofia.Boquist@sva.se

Anuska Irma Bori

Universität Leinzig

Leipzig, Germany

bori@vetmed.uni-leipzig.de

Peter Braam

World Health Organization

Geneva, Switzerland

braamp@who.int

Eric Breidenbach

Bundesamt für Veterinärwesen

Bern-Liebefeld, Switzerland

Eric.Breidenbach@bvet.admin.ch

Frank Brendel

Berlin, Germany

fbrendel@sbnafu.de

Joyce Brown

Food Standards Agency UK

London, Great Britain

Joyce.Brown@foodstandards.gsi.gov.uk

Iuliane Bräunig

BfR (Bundesinstitut für Risikobewertung)

Berlin, Germany

juliane.braeunig@bfr.bund.de

Robert L. Buchanan

FDA CFSAN (US Food and Drug

Administration, Center for Food Safety and

Applied Nutrition)

College Park MD, USA

robert.buchanan@fda.hhs.gov

Marion Castle

Food Standards Agency

London, Great Britain

Marion.castle@foodstandards.gsi.gov.uk

Jean-Charles Cavitte

European Commission, Research Directorate General Directorate E - Biotechnology, Agriculture and

Food

Brussels, Belgium

Jean-Charles.Cavitte@cec.eu.int

Scott Crerar

Centre for Food Safety, Food and Environmental Hygiene Department Hong Kong, China screrar@fehd.gov.hk

Corinne Danan

AFSSA (Agence Française de Sécurité Sanitaire des Aliments) Maisons-Alfort, France c.danan@afssa.fr

Julie David

AFSSA (Agence Française de Sécurité Sanitaire des Aliments) Fougères, France j.david@afssa.fr

Jennie Drew

Society for Applied Microbiology Bedford, Great Britain teresa@sfam.org.uk

Yvonne van Duynhoven

National Institute for Public Health and the Environment Bilthoven, The Netherlands Y.van.Duynhoven@rivm.nl

Dörte Döpfer

Quantitative Veterinary Epidemiology Group Animal Sciences Group, Wageningen UR Division of Infectious Diseases Lelystad, The Netherlands dorte.dopfer@wur.nl

Lüppo Ellerbroek

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany lueppo.ellerbroek@bfr.bund.de

Olivier Espeisse

ELI LILLY Brussels, Belgium espeisse_olivier@lilly.com

Steen Ethelberg

Statens Serum Institut Copenhagen S., Denmark set@ssi.dk

Eric Evers

National Institute for Public Health and the Environment Bilthoven, The Netherlands Eric.evers@rivm.nl

Gerhard Falkenhorst

Statens Serum Institut Copenhagen, Denmark GFA@ssi.dk

Christina Frank

Robert Koch-Institut Berlin, Germany FrankC@rki.de

Miriam Friedemann

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany m.friedemann@bfr.bund.de

Dennis Fryback

University of Wisconsin-Madison Madison WI, USA dfryback@wisc.edu

Hans Fröder

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany Hans.froeder@bfr.bund.de

Peter Gerner-Smidt

CDC (Centers for Disease Control and Prevention) Atlanta GA, USA Plg5@cdc.gov

Andrea Gervelmeyer

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany a.gervelmeyer@bfr.bund.de

Monica Virginia Gianfranceschi

National Center for Food Quality and Risk Assessment – National Health Institute Rome, Italy Monica.gianfranceschi@iss.it

Ruth Gilbert

Institute of Child Health London UK WC1N 1EH, Great Britain r.gilbert@ich.ucl.ac.uk

Chuanfa Guo

U.S. Department of Agriculture Food Safety and Inspection Service Washington DC, USA Chuanfa.guo@fsis.usda.gov

Tine Hald

Danish Institute for Food and Veterinary Research Soberg, Denmark tih@dfvf.dk

Ahmad Hamedy

Universität Leipzig Leipzig, Germany hamedy@vetmed.uni-leipzig.de

Craig Harris

Food Safety Policy Center Michigan State University Lansing, MI, USA harrisc@msu.edu

Matthias Hartung

Bundesinsitut für Risikobewertung Berlin, Germany matthias.hartung@bfr.bund.de

Steve Hathaway

New Zealand Food Safety Authority Wellington, Neuseeland Steve.hathaway@nzfsa.govt.nz

Arie Havelaar

RIVM Bilthoven, The Netherlands

Arie.havelaar@rivm.nl

Walther Heeschen

Journalist Kiel, Germany heeschen@t-online.de

Morten Helms

Statens Serum Institut Copenhagen S, Denmark helms@dadlnet.dk

Reiner Helmuth

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany r.helmuth@bfr.bund.de

Michaela Hempen

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany Michaela.Hempen@bfr.bund.de

Andreas Hensel

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany hensel@bfr.bund.de

Petra Hiller

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany p.hiller@bfr.bund.de

Roxan Hooshangi

Canadian Mission to the European Union Brussels, Belgium Roxan.Hooshangi@international.gc.ca

Helmut Hotzel

Friedrich-Loeffler-Institut Jena, Germany helmut.hotzel@fli.bund.de

Stephan Hühn

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany Stephan.huehn@bfr.bund.de

Katri Jalava

Health Protection Agency Centre for Infections London NW9 5EQ, Great Britain pauline.francis@hpa.org.uk

Andreas Jansen

Robert Koch-Institut Berlin, Germany JansenA@rki.de

Karsten Klint Jensen

Danish Centre for Bioethics and Risk Assessment Frederiksberg C, Denmark kkj@foi.dk

Jan van Kooij

Food and Product Safety Authority The Hague, The Netherlands jan.van.Kooij@vwa.nl

Gérard Krause

Robert Koch-Institut Berlin, Germany KrauseG@rki.de

Gladys Krause

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany gladys.krause@bfr.bund.de

Alan J. Krupnick

Resources for the Future Washington DC 20036, USA Krupnick@rff.org

Annemarie Käsbohrer

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany annemarie.kaesbohrer@bfr.bund.de

Renaud Lailler

AFSSA (Agence Française de Sécurité Sanitaire des Aliments) Maisons-Alfort, France r.lailler@afssa.fr

Rob Lake

Institute of Environmental Science and Research Ltd. Christchurch, Neuseeland rob.lake@esr.cri.nz

Katrin Leitmeyer

Robert Koch-Institut Berlin, Germany LeitmeyerK@rki.de

Sébastien Lesterle

AFSSA (Agence Française de Sécurité Sanitaire des Aliments) Maisons-Alfort, France s.lesterle@afssa.fr

Alies van Lier

RIVM (National Institute for Public Health and the Environment) BA Bilthoven, The Netherlands alies.van.lier@rivm.nl

Ruff Lowman

Canadian Food Inspection Agency Ottawa, Ontario K2H 8P9, Canada rlowman@inspection.gc.ca

Petra Luber

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit Berlin, Germany petra.luber@bvl.bund.de

Pia Makela

EFSA (European Food Safety Authority) Parma, Italy Pia.makela@efsa.eu.int

Pradeep Malakar

Institute Food Research Norwich, Great Britain Pradeep.malakar@bbsrc.ac.uk

Burkhard Malorny

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany b.malorny@bfr.bund.de

Marie-Josée Mangen

(RIVM) National Institute for Public Health and the Environment Bilthoven, The Netherlands marie-josee.mangen@rivm.nl

Anne Mazick

Statens Serum Institut Copenhagen S, Denmark maz@ssi.dk

Kare Molbak

Statens Serum Institut Copenhagen, Denmark krm@ssi.dk

J. Glenn Morris, Jr.

University of Maryland, Baltimore Baltimore, MD, USA ksantoni@epi.umaryland.edu

Gemma Mulholland

Department for Environment Food and Rural Affairs London SW1P 4PQ, Great Britain gemma.mulholland@defra.gsi.gov.uk

Christine Müller-Graf

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany christine.mueller-graf@bfr.bund.de

Diane Newell

Veterinary Laboratories Agency New Haw Addlestone KT15 3NB, Great Britain d.newell@vla.defra.gsi.gov.uk

Gordon Nichols

Communicable Disease Surveillance Centre London NW9 5EQ, Great Britain Gordon.Nichols@hpa.org.uk

Karsten Nöckler

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany karsten.noeckler@bfr.bund.de

Sarah O'Brien

University of Manchester Clinical Sciences Building, Hope Hospital Salford, M6 8 HD, Great Britain Sarah.o'brien@manchester.ac.uk

Kanyin Liane Ong

CDC (Centers for Disease Control and Prevention)
Atlanta GA 30333, USA
enn1@cdc.gov

Wim Ooms

VWA (Food and Consumer Product Safety Authority) CM Den Haag, The Netherlands wim.ooms@vwa.nl

John Painter

CDC (Centers for Disease Control and Prevention) Foodborne and Diarrheal Diseases Branch Atlanta GA, USA ipainter@cdc.gov

Katarzyna Pancer

National Institute of Hygiene Warsaw, Poland kpancer@pzh.gov.pl

Mara Paniconi

Istituto Superiore Di Sanità Roma, Italy mara.paniconi@iss.it

Greg Paoli

Decisionalysis Risk Consultants, INC. K1H 6S3 Ottawa, Ontario, Canada gpaoli@AnalyzeRisk.com

Wilfrid van Pelt

RIVM BA Bilthoven, The Netherlands W.van.Pelt@rivm.nl

Sara Pires

Danish Institute for Food and Veterinary Research Copenhagen, Denmark smpxy@dfvf.dk

Lars Plym Forshell

National Food Administration Uppsala, Sweden lars.plym.forshell@slv.se

Gabriele Poggensee

Robert Koch-Institut Berlin, Germany PoggenseeG@rki.de

Tobin Robinson

EFSA (European Food Safety Authority) Parma, Italy tobin.robinson@efsa.europa.eu

Juliana Ruzante

University of California Davis CA, USA jmruzante@ucdavis.edu

Elaine Scallan

CDC (Centers for Disease Control and Prevention) Atlanta GA, USA escallan@cdc.gov

Gaia Scavia

ISS

Roma, Italy gscavia@iss.it

Katrin Schmidt

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany katrin.schmidt@bfr.bund.de

Carl Schroeder

USDA FSIS (U.S. Department of Agriculture, Food Safety and Inspection Service)
Washington DC, USA
Carl.Schroeder@fsis.usda.gov

Andreas Schroeter

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany a.schroeter@bfr.bund.de

Ingrid Schütt-Abraham

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany Ingrid.Schuett-Abraham@bfr.bund.de

Craig Shadbolt

New South Wales Food Authority Newington, New South Wales, Australien Craig.Shadbolt@foodauthority.nsw.gov.au

Kris De Smet

European Commission DG Sanco Brussels, Belgium Kris.de-smet@cec.eu.int

Gary Smith

University of Pennsylvania School of Veterinary Medicine, New Bolton Center Kennett Square PA, USA garys@vet.upenn.edu

Emma Snary

Veterinary Laboratories Agency Surrey, Great Britain E.L.Snary@yla.defra.gsi.gov.uk

Klaus Stark

Robert Koch-Institut Berlin, Germany StarkK@rki.de

Pawel Stefanoff

National Institute of Hygiene Warsaw, Poland pstefanoff@pzh.gov.pl

Inge Stoelhorst

Ministry of Health, Welfare and Sports Den Haag, The Netherlands i.stoelhorst@minvws.nl

Elisabetta Suffredini

Istituto Superiore Di Sanità Roma, Italy elisabetta.suffredini@iss.it

Nedzib Tafro

Dutch Food Authority, Border Inspection Post Schiphol, The Netherlands nedzib.tafro@vwa.nl

Michael Taylor

University of Maryland School of Medicine Baltimore MD, USA mtaylor@epi.umaryland.edu

Benno Ter Kuile

Netherlands Food and Consumer Product Authority The Hague, The Netherlands Benno.ter.kuile@vwa.nl

Anne Thébault

AFSSA-DERNS Maisons-Alfort, France c.evans@dg.afssa.fr

Ewen Todd

Michigan State University Lansing MI, USA toddewen@cvm.msu.edu

Anja Vespermann

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany anja.vespermann@bfr.bund.de

Antonio Vieira

Danish Institute for Food and Veterinary Research Soborg, Denmark avixx@dfvf.dk

Duc Vugia

California Department of Health Services, Infectious Deseases Branch Richmond CA, USA DVUGIA@DHS.CA.GOV

Helene Wahlström

National Veterinary Institute Uppsala, Sweden helene.wahlstrom@sva.se

Christina Weber

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany Christina.Weber@bfr.bund.de

Ole Wichmann

Robert-Koch Institut Berlin, Germany wichmanno@rki.de

Heidi Wichmann-Schauer

BfR (Bundesinstitut für Risikobewertung) Berlin, Germany heidi.wichmann-schauer@bfr.bund.de

Miriam Wolf

Central Laboratories Friedrichsdorf Friedrichsdorf, Germany miriam.wolf@milupa.de