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Editorial note to the special issue "Risk factors for sporadic foodborne diseases by meta-analysis of observational studies"

Epidemiological studies are valuable tools for investigating the origin of outbreaks and also sporadic cases in order to better understand the circumstances of foodborne disease occurrence. It is common to report *ad hoc* analyses of compiled data of food-borne disease outbreaks, however, such analyses including sporadic cases remain relatively rare. In the literature, several case-control and cohort studies have been published that investigate associations of sporadic foodborne diseases with diverse exposure pathways, foods, food handling practices and health pre-conditions in different populations.

This special issue compiles several epidemiological studies of sporadic cases of leading foodborne infectious diseases, and summarises the measurements of associations (odds ratios) of risk factors with the occurrence of sporadic cases. These odds ratio estimates in combination with the frequency of exposure to risk factors will allow the contributions of the different risk factors to be assessed based on calculations of attributable fractions. Source attribution has been traditionally accomplished by different methods such as epidemiological studies, microbial subtyping models, comparative exposure assessments and expert's knowledge elicitation. Yet, there has been very few publications using meta-analysis to better understand risk factor identification and help prioritize and quantify interventions measures to reduce the impact of foodborne diseases.

From 2016 to 2019, researchers from the French Agency for Food, Environmental and Occupational Health & Safety (Anses) and the Mountain Research Centre (CIMO) of the Polytechnic Institute of Bragança, Portugal, performed meta-analysis studies under the collaborative project "Risk factors of sporadic infections linked to foodborne biological hazards." The objectives of this meta-analysis project were to:

1) Map all relevant literature reporting the results of observational studies on risk factors associated with eleven foodborne diseases; non-typhoidal *Salmonella* spp., *Campylobacter* spp., *Listeria monocytogenes*, shigatoxin-producing *Escherichia coli* (STEC), *Yersinia enterocolitica, Cryptosporidium* spp., *Giardia duodenalis, Toxoplasma gondii*, Hepatitis A virus (HAV), Hepatitis E virus (HEV) and Norovirus
2) Combine the evidence from quality studies on the risks of acquiring these diseases from exposure to different sources; and
3) Obtain a better understanding of the advantages and limitations of statistical synthesis of case-control and cohort data.

Our meta-analysis project incorporated case-control and cohort studies of sporadic infections, as opposed to outbreak studies. The main results from this project are presented in the publications of this Special Issue, with our first article (Gonzales-Barron et al., 2019) explaining in detail the scheme adopted for systematic review of observational studies, including the broad search strategy criteria and the methodological quality assessment of primary studies. To overcome the well-known meta-analysis limitation related to low quality studies that result in biased or incorrect results, we focused on the key methodological issues crucial to the validity of the outcomes of a case-control/cohort study: case definition, selection of control groups and data analysis. We propose a hierarchical meta-regression approach that extracts the between-study variability in the association measure (odds ratio, OR), and the heterogeneity by type of analysis and model (i.e., ORs estimated in univariate analysis and multivariate analysis with different adjustment factors), in order to produce less biased pooled OR estimates. When possible, meta-regressions evaluated different populations separately (general population, children, and susceptible populations). In order to support the integration of outcomes from the observational studies, a broad data categorisation scheme was developed to hierarchically group the risk factors into travel, host-specific factors and pathways of exposure. This was done with views to harmonise the distinct labels assigned by the primary studies to the potential determinants of disease, and to produce a unified approach yet flexible enough to support pathogen-specific variations in data categorisation. The first article "Strategy for Systematic Review of Observational Studies and Meta-Analysis Modelling of Risk Factors for Sporadic Foodborne Diseases" presents the general methodology for information retrieval and summarization applied in all the other articles published in this Special Issue.

Five articles of the Special Issue deal with the risk factors for foodborne diseases transmitted by bacteria. Fravalo et al. (2020) found that the odds of acquiring campylobacteriosis in the mixed population increased significantly with international travel, followed by recent use of gastric antacids, occupational exposure to animals or carcasses, and food consumption (in particular raw or undercooked eggs, poultry, beef, and dairy). Children were more prone to acquire campylobacteriosis through environmental and animal transmission routes, such as drinking untreated water, exposure to recreational water, exposure to farm/rural environment, and contact with farm animals. Leclercq et al. (2020) corroborated that the main risk factor for acquiring listeriosis is suffering from an immunocompromising disease; and confirmed known risk factors, such as consumption of RTE dairy, seafood and processed meat, and underlined new food vehicles, such as fruits and vegetables. In susceptible and non-perinatal populations, the food categories followed a similar ranking as sources of listeriosis: seafood, diary, composite foods, produce and meat, in decreasing order. Furthermore, susceptible

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people who claimed having eaten raw processed meats or undercooked poultry or having eaten out at an establishment had significantly increased odds of acquiring listeriosis.

In Guillier et al. (2020), the meta-analysis of case-control studies helped identifying important food sources for acquiring salmonellosis, such as consumption of eggs and eggs products, composite foods and meat (pork, red meats other than beef and poultry meats) in the mixed population. In children, the main risk factors were person-to-person transmission, recent use of gastric anti-acids or antibiotics, contact with pets and farm animals, environmental routes, and food vehicles such as milk formula, produce, meat and egg products. The meta-analysis on case-control studies of sporadic infections caused by STEC, conducted by Augustin et al. (2020), highlights international travel, person-to-person contagion, contact with farm animals, untreated drinking water, and consumption of undercooked beef, ready-to-eat meat and composite foods as the main risk factors of the disease. Surprisingly, produce (fruits/vegetables) was not found to be associated with sporadic STEC infection, but poultry meat and fish were. Guillier et al. (2020), in their research synthesis of factors for sporadic yersiniosis, confirmed the role of undercooked pork and stressed the importance of routes of transmission other than food, such as occupational exposure to pigs and drinking untreated water in the mixed population, and playground exposure in children. Nevertheless, chronic diseases in the mixed population are as a whole the most important risk factors for acquiring yersiniosis.

In relation to the foodborne diseases transmitted by viruses, three meta-analysis studies were conducted on the risk factors for HAV, HEV and norovirus. Combining the outcomes from case-control, cohort and transversal studies of HAV, the highest pooled ORs were found for international travel and person-to-person contagion in both the general population and children. Dietary risk factors, such as consumption of produce, seafood, composite dishes prepared outside home, and environmental pathways such as drinking untreated water and contact with wastewater were strongly associated with HAV infection. Pavio et al. (2020) synthesized the results from observational studies on risk factors for HEV infection, and identified that parenteral pathways (blood transfusion, tattooing, intra-venous injection or dialysis) and transmission pathways related to contaminated water, occupational exposure to animals and consumption of pig meat, and preparations containing pig liver and game meat are all significant risk factors for HEV infection. In particular, consuming pig meat improperly cooked increases the odds of acquiring hepatitis E. The meta-analysis on risk factors for sporadic norovirus infection, performed by Thebault et al. (2020), corroborated that oral-fecal routes and lack of hygiene are the main sources of disease. Other important transmission routes are the indirect ones such as untreated water, farm environment and the food pathways – seafood and composite food.

Meta-analyzed sources of foodborne diseases transmitted by parasites are presented in three articles. Foreign travel and factors related to feco-oral transmissions (such as person-to-person transmission, lack of personal hygiene, contact with animals and contaminated water) were found significant for both cryptosporidiosis and giardiasis. Kooh et al. (2020) showed that the consumption of meat, dairy products (raw milk) and dishes consumed outside home were significantly associated with cryptosporidiosis. Concerning the food exposures, Thebault et al. (2020) pointed out that composite foods and unwashed vegetables are significantly associated with giardiasis. The meta-analysis on risk factors for toxoplasmosis, undertaken by Thebault et al. (2020), allowed the thorough investigation of mixed population (930 ORs), pregnant women (841 ORs) and children (185 ORs). They revealed that contact with soil and contact with animals, in particular cats, increased the odds of acquiring *Toxoplasma* infection. In addition to meat categories – pork, poultry, beef, processed meat, lamb and game meat – shellfish and raw milk were also identified as significant risk factors. In pregnant women, other important determinants of the infection were travelling abroad and blood transfusion.

The main limitations of the meta-analyses were linked in particular to the normal heterogeneity and lack of information of primary studies, which are briefly outlined as follows:

- With regards to the definition of cases, in few studies, the diagnostic of some cases was lab-confirmed while others were based on clinical symptoms. For some hazards (e.g., HAV, HEV and *T. gondii*), the case definition was based on infection (identified through serological assays) associated or not with clinical symptoms. Since seropositive individuals correspond to asymptomatic cases or past infections, there may be a substantial lapse of time between contamination and the collection of information on the exposures of infected persons during studies. This meta-analysis advises that symptomatic cases of these diseases should be more investigated in epidemiological studies as it would allow the identification of specific risk factors (e.g. host susceptibility, exposure to higher dose, strain virulence).
- The majority of studies investigated the disease caused by undifferentiated species or subtypes, so that it was not possible to conduct a meta-analysis of risk factors related to specific species or subtypes. Distinct genetic species/strains can be found to be associated with distinct geographical area (e.g. genotypes of HEV, strains of *T. gondii*) or specific host *(C. parvum/hominis*, serotypes of *Salmonella, Campylobacter*). Subtyping of human isolates included in case-control studies could allow the identification of risk factors specific to species or subtypes.
- Moreover, in the framework of source attribution, the population attributable risk fraction (PAF) needs to be estimated from epidemiological studies. Overall, only 11% of the primary studies provided a PAF. Therefore, a ranking of risk factors based on meta-analysed pooled PAF could not be directly done, and confirmation is needed by epidemiological studies at national or regional level.
- International travel has been identified as an important risk factor for many of the foodborne diseases; nonetheless, due to the lack of information on destination countries in the questionnaires, it was not possible to identify regions at particular risk. Most of the observational studies focused on the general or mixed population, so there is also a need to conduct more studies on elderly and immunocompromised individuals.
- Food production or consumption patterns could be different between countries. Consumption practices may be very country-specific for certain food categories (e.g. consumption of raw minced pork, raw milk cheese). Consequently, the risk factors identified are not necessarily relevant for some specific countries. However, this diversity of situations can reveal the potential of certain foods to carry the pathogen when certain practices (pasteurization, cooking, washing) are not applied. Furthermore, in the context of food globalization, it could give an indication for the monitoring of imported products.

The integration of the results from 673 observational studies compiled in this Special Issue allowed us to study different populations separately, and helped identify new potential risk factors that are supported by outbreaks or biological knowledge. In addition, we identified risk factors specific to certain foodborne diseases, and unexpected risk factors, such as eggs and egg products as source of campylobacteriosis or poultry meat as source of STEC infection. This comprehensive meta-analysis study also provided valuable insights for the design of future observational studies. For instance, the broad definition of exposure factors greatly limits the interpretation of results, and therefore future case-control studies should investigate more precisely the different categories, such as consumption of leafy greens instead of consumption of vegetables, or consumption of shellfish instead of seafood. Also, more information on cooking or washing practices in relation to duration or frequency of exposure should be obtained. In summary, and despite some limitations, this Special Issue is the first work of its kind and provides a comprehensive overview of food and non-food related factors

associated with eleven biological hazards, which can be used to inform risk managers, guide future epidemiological studies and establish public health recommendations.

Ursula Gonzales-Barron[a,*], Vasco Cadavez[a], Anne Thebault[b], Pauline Kooh[b], Moez Sanaa[b]

[a] *Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolónia, Bragança 5300-253, Portugal*

[b] *Risk Assessment Department, French Agency for Food, Environmental and Occupational Health & Safety (Anses), 14 rue Pierre et Marie Curie Maisons-Alfort, France*

[*] Corresponding author.
E-mail address: ubarron@ipb.pt (U. Gonzales-Barron).