Risk factors for sporadic cryptosporidiosis: A systematic review and meta-analysis

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Highlights

- 57 studies on sporadic cryptosporidiosis cases were included in the meta-analysis
- Travel abroad and immunocompromising conditions were important risk factors
- Contact with infected humans and animals and contaminated water increased the risk
- Consumption of meat, raw milk, and composite foods was associated with the illness

Abstract

Cryptosporidium spp. is an important cause of gastrointestinal disease worldwide, responsible for 69 million cases of illness in 2016. Information on the sources and transmission pathways of human cryptosporidiosis results mainly from outbreak investigations.

A systematic review and a meta-analysis of case-control and cohort studies were performed to determine the main risk factors associated with sporadic cryptosporidiosis. Suitable scientific articles were identified through a systematic literature search and subjected to a methodological quality assessment. From each study, odds ratio (OR) measures were extracted/ calculated, as well as study characteristics such as population type, design, type of model and risk factor hierarchy. Mixed-effects meta-analysis models were adjusted by population type to appropriate data partitions.

From 1985 identified references, the quality assessment stage was passed by 57 – cohort and case-control studies – focusing on sporadic cryptosporidiosis. The eligible studies were conducted between 1983 and 2016 and provided 568 OR categorized for meta-analysis.

This meta-analysis identified travel, immunocompromising conditions, contact with infected humans, waterborne transmission (contact with recreational waters, wastewater, and consumption of untreated drinking water), contact with animals and food consumption as the relevant risk factors for sporadic cryptosporidiosis. With regards to food exposures, consumption of meat, dairy products (raw milk) and dishes consumed outside home were found significantly associated with cryptosporidiosis. The consumption of poorly washed fruits and vegetables significantly increases ORs. This meta-analysis reveals that some potential sources of *Cryptosporidium* such as shellfish or vegetables are under-investigated.

Future case-control studies for sporadic cryptosporidiosis should include population at risk, and investigate other potential sources in relation to the genotype and the subtype of *Cryptosporidium* spp.

Keywords: *Research synthesis; case-control studies; cohort studies; meta-regression; Cryptosporidium*

1. Introduction

Cryptosporidium spp. is a protozoan parasite that belongs to Apicomplexa phylum. *Cryptosporidium* spp. is a well-known causative agent of gastrointestinal diseases and commonly identified in humans and animals, including livestock and particularly cattle (calves). The main symptom of human cryptosporidiosis is diarrhea that may be responsible for weight loss and dehydration in immunocompetent, but immunocompromised patients are at increased risk of developing a severe disease (Hunter and Nichols, 2002).

Cryptosporidium spp. are globally distributed, responsible for 69 million cases of illness, and 57,203 deaths in 2016 (Troeger et al., 2018). Kirk et al. (2015) estimated that cryptosporidiosis resulted in 2,159,331 DALYs in 2010. A clinical and epidemiological study involving 22,500 children from Africa and Asia revealed that *Cryptosporidium* spp. is one of four pathogens responsible for most of moderate to severe diarrhea in infants and toddlers (Kotloff et al., 2013). In 2016, *Cryptosporidiosis* was estimated to account for 10% of cases of diarrhea mortality among children under 5 years old (Troeger et al., 2018).

There are numerous species and genotypes of *Cryptosporidium*, but human infection involves mainly two species: *Cryptosporidium hominis,* whose main host is humans and C*ryptosporidium parvum* which infects animal and ruminants. Transmission can occur through the fecal-oral route, involving direct (person-to-person transmission or contact with animals) and indirect (waterborne or foodborne) pathways.

Water is the principal vector of contamination of *Cryptosporidium* and, numerous waterborne outbreaks involving both drinking water and recreational waters have been reported (Moreira and Bondelind, 2017; Ryan et al., 2017). Over the past years, foodborne outbreaks of cryptosporidiosis have been increasingly reported involving a diversity of food products (Ryan et al., 2018). Outbreaks investigations provide useful information about sources and transmission pathways of human cryptosporidiosis. Nevertheless, cryptosporidiosis cases are underreported or underdiagnosed in most countries (ECDC, 2019; Haagsma et al., 2013).

Several epidemiological studies of sporadic cryptosporidiosis have been published. A systematic review and a meta-analysis of case-control and cohort studies were performed to determine the main risk factors associated with sporadic cryptosporidiosis. Characterization of risk factors will contribute to identifying measures to reduce the burden of cryptosporidiosis.

2. Material and methods

The protocol of the systematic review and the meta-analysis model are described in depth in the methodological paper of this special issue (Gonzales-Barron et al., 2019).

2.1 Systematic review

The literature search was conducted in March 2017 using a combination of keywords related to (1)"*Cryptosporidium"* "OR" "cryptosporidiosis", (2) "case-control" "OR" "risk factor" "OR" "cohort" (3) "infection" "OR" "disease", joined by the logical connector "AND". Relevant studies were identified from five bibliographic search engines, Science Direct, PubMed, Scielo, ISI Web of Science and Scopus. No restrictions were defined for the year of the study or type of publication. The search was limited to the languages English, French, Portuguese and Spanish.

Each reference record was screened for relevance for inclusion in the meta-analysis study. The methodological quality of the "candidate" studies was assessed using pre-set quality criteria, comprising (1) appropriate selection of the controls; (2) adjustment to correct for confounders, (3) comparability between cases and controls, (4) acceptable responses rates for the exposed and control groups; (5) data analysis appropriate to the study design; (6) provision of odds ratio (OR) with confidence interval or p-value; or provision of sufficient data to calculate ORs; overall quality of the study (Gonzales-Barron et al., 2019). Primary studies that passed the screening for relevance were marked as having a potential for bias if they failed to meet at least one of the methodological quality assessment criteria.

Data from primary studies were then extracted using a standardized spreadsheet. Data extracted included the relevant study characteristics (location, period, population, case definition, design, sample size of the groups, type of model, etc.), the categorized risk factors, the setting, the handling practices and the outcome of the study (ORs).

A data categorization scheme was established to hierarchically group the risk factors into travel, host-specific factors and, pathways of exposure (i.e., person-to-person, animal, environment, and food routes) (see the methodological paper of this issue). In addition to the standard risk factors, the class "Hygiene" (e.g. "no handwashing after toilet", "poor hygiene habits") was also used. Person-to-person transmission was stratified in three classes: contact in the household, contact in the community and sexual transmission. The variable "**Population**" was stratified into mixed (adults or undefined), children (under 16 years old) and susceptible (HIV infection, AIDS, elderly population).

2.2 Data synthesis

The joint meta-analytical data was first described using basic statistics. Next, data was partitioned into subsets of categories of risk factors. The meta-analytical models were then fitted to each of the data partitions or subsets to estimate pooled OR related to travel, host-specific factors and transmission pathways related to person-to-person contagion, animal contact, environmental exposures, and food vehicles. The meta-analytical models were fitted separately by population type. For some food classes, the effects of food preparation (e.g, eating raw, undercooked) and setting (i.e., eating food prepared outside the home) on the pooled OR were assessed by calculating the ratio of the mean OR when food is mishandled to the base OR.

The statistical analysis was designed to assess the effect of the geographical region, the study period and the analysis type (univariate/multivariate) on the final result. The objective of the region-specific meta-analysis was to inform the decision on whether the geographical regions were to be maintained for the subsequent pooling of ORs. A geographical region (Asia, North America, South America, Africa, Europe, Oceania) was removed from a particular meta-analysis partition only if its pooled ORs were different from those associated with the other regions, or if less than 3 ORs represented the region (Gonzales-Barron et al., 2019)

All meta-analytical models were essentially weighted random-effects linear regression models. Once a meta-analysis model was fitted, influential diagnostics statistics were applied to remove any influential observation originating from studies marked as having a potential for bias. Publication bias was assessed by funnel plots and a statistical test investigating the effect of the study sample size on the ORs (Tables 2, 3 and 4) (Gonzales-Barron et al., 2019). Heterogeneity between studies was assessed by different indicators such as the between-study variability (τ^2), the QE test investigating residual heterogeneity, the variance of residuals and the intra-class correlation I^2 (Gonzales-Barron et al., 2019). Publication bias and remaining heterogeneity were not further corrected for, but were taken into account for the interpretation of the results.

All analyses were carried out in the R software (R Development Core Team, 2008) implemented with the *metafor* package (Viechtbauer, 2010).

The meta-analyzed risk factors are presented in summary tables only when significant. Pooled ORs were considered significant when the lower bound of the 95% confidence interval (CI) was equal or greater than 1.0, except for breastfeeding where the upper bound of the confidence interval had to be below 1 for it to be deemed as significant (protective effect).

3. Results

3.1 Descriptive statistics

From 1985 identified references, the quality assessment stage was passed by 57 primary studies – cohort and case-control studies – focusing on sporadic cryptosporidiosis (Figure 1). These published studies were conducted between 1983 and 2016. Table 1 and Appendix 1 compile the list of the primary studies along with their main features. The eligible studies jointly provided 568 odds-ratios categorized for meta-analysis. Meta-analytical data were obtained from primary studies conducted in 31 countries, although studies from only 5 countries generated ~70% of the ORs retrieved. These were: USA (9 studies -136 ORs), UK (3 studies - 79 ORs), Australia (3 studies - 66 ORs), the Netherlands (2 studies - 66 ORs) and Canada (2 studies - 47 ORs).

Primary studies investigated risk factors in different types of population, namely children (27 studies), mixed population (24 studies) and susceptible population, which included immunocompromised individuals (8 studies) and elderly population (1 study). Separate meta-analyses were then adjusted on the mixed population (382 ORs), children (117 ORs) and susceptible (69 ORs). Most studies investigated illness caused by any *Cryptosporidium* species (49) or by *C. parvum* without distinction between *C. parvum* and *C. hominis*. Few studies investigated cases caused by *C. parvum* (3*)* or *C. hominis* (1). In all studies, the symptomatic cases of cryptosporidiosis were laboratory-confirmed.

With regards to the risk factor classes, sporadic illness investigations focused more on multiple pathways of exposure: environment (222 ORs), contact with animals (114 ORs), food (80 ORs), person to person (78 ORs). Host-specific factors (47 ORs), personal hygiene (4 ORs) and travel (23 ORs) were also investigated.

During methodological quality assessment, potential for selection bias status was assigned to six case-control studies since, in those, the controls were not healthy individuals but people affected by another enteric disease such as giardiasis (Firdu et al., 2014; Redlinger et al., 2002), salmonellosis (Marder, 2012), amoebiasis (Ravel et al., 2013), campylobacteriosis (Wilson et al., 2008), and one of nine other enteric infections (Pintar et al., 2009). As it is not clear whether these controls shared routes of exposure with the case patients, the ORs extracted from the aforementioned studies were marked as having potential for selection bias. These case-control studies provided 84 potentially-biased ORs whose influence on the meta-analyzed OR estimates was appraised by means of the Cook's distance.

Only 13 case-control studies employed a matched experimental design (Table 1). Bringing together the matched and unmatched designs, 379 ORs (67% of the data) were not adjusted by

any confounder (crude ORs) (e.g. age, sex, other risk factors), while 189 ORs (33%) were adjusted using either Mantel-Haenzel or logistic regressions.

3.2 **Meta-analysis**

The meta-analysed significant risk factors are presented in summary tables (Tables 2 and 3). Non-significant results on the main risk factors are presented in Appendix 2. More detailed descriptive results, in particular, funnel plots, forest plots, and OR of non-significant results, are in a complete report available upon request.

Meta-analysis for travel

According to this meta-analysis, **foreign travel** is an important risk factor for acquiring cryptosporidiosis. For residents of USA, UK, Switzerland, Netherlands, Australia and New Zealand, traveling abroad increased their odds of acquiring cryptosporidiosis (pooled OR=4.216; 95% CI [2.529 - 7.029]) (Table 2; Figure 2).

Meta-analysis for host-specific risk factors

The meta-analysis on **host-specific factors** showed that immunocompromising conditions were associated with cryptosporidiosis for the mixed, children with pooled ORs ranging from 2.721 to 4.507. For the mixed and children population, immunocompromising conditions included HIV infection, other immune system illnesses, the use of immunosuppressive medication, etc. Other medical conditions, including chronic disease and HBV infection, were also found to be associated with cryptosporidiosis in the mixed population (pooled OR=2.392; 95% CI [1.588 - 3.604]).

Meta-analysis for person to person transmission factors

Person-to-person transmission was a significant risk factor of acquiring cryptosporidiosis for all the populations (pooled OR ranging from 1.903 to 3.786; Table 2; Figure 3). The same data set related to person-to-person transmission was stratified in three classes according to the type or the location of the contact. Significant associations were found for contact in household (pooled OR=2.191; 95% CI [1.771-2.711]), contact in the community (pooled OR=3.339; 95% CI [2.623- 4.243]) and sexual transmission (pooled OR =2.350; 95% CI [1.439- 3.837]).

Poor personal hygiene (e.g “no handwashing after toilet”, “ poor hygiene habits”) could be a risk factor for cryptosporidiosis (pooled OR=1.736; 95% CI [1.286- 2.343]).

Meta-analysis for animal contact

Contact with animals was associated with an increased risk of cryptosporidiosis. Significant associations were found for farm animals in the mixed population (pooled OR=2.167; 95% CI [1.703-2.758]; figure 4) and children (pooled OR=1.968; 95% CI [1.284- 3.018]) and pets in children (pooled OR= 1.694; 95% CI [1.297 - 2.212]).

Meta-analysis for environmental factors

In both the mixed and children populations, **the environmental pathways** under study were significantly associated with cryptosporidiosis: recreational water (pooled OR = 1.968; 95% CI [1.475- 2.625] for the mixed population (figure 5); pooled OR=4.114; 95% CI [1.579-10.715] for children); farm environment (pooled OR=1.794; 95% CI [1.444- 2.230] for the mixed population and pooled OR=1.802; 95% CI [1.194- 2.719] for children), attendance to daycare (pooled OR=1.539; 95% CI [1.429- 1.659] for the mixed population and pooled OR=1.742; 95% CI [1.031- 2.945] for children), untreated drinking water (pooled OR=1.358; 95% CI [1.249- 1.475] for the mixed population and pooled OR=1.367; 95% CI [1.092-1.712] for children) and wastewater (only in the mixed population: pooled OR=1.697; 95% CI [1.127- 2.555]). Data from Oceania (2 ORs) were removed from the children population. This exclusion only affects the significance of the OR related to attendance to daycare.

Meta-analysis for food consumption

The meta-analysis on **food consumption** pathways revealed significant associations with mea t (pooled OR=1.934; 95% CI [1.236 - 3.024]; Figure 6) and dairy (pooled OR=1.533; 95% CI [1.009- 2.329]; Figure 7) for the mixed population, and composite foods (pooled OR=1.532; 9 5% CI [1.072- 2.189]) for children. Within the food vehicles, associations with cryptosporidio sis were observed for: barbecue foods (pooled OR=2.005; 95% CI [1.624- 2.476]), meat of no n-specified origin ("Others"; pooled OR=1.991; 95% CI [1.288- 3.080]), dishes prepared outs ide the home (pooled OR=1.717; 95% CI [1.220-2.416]) and milk (comprising essentially raw milk in this category) (pooled OR=1.509; 95% CI [1.071- 2.125]). If we restrict the analysis t o raw milk, combining ORs in population mixed and children with 7 OR, the raw milk is still significant at a pooled OR of 1.670 (95% CI [1.035 - 2.695]).

Food categories that on meta-analysis had a non-significant association with cryptosporidiosis were produce (comprising raw or fresh vegetables (10 ORs) and unwashed fruits (1 OR) and beverage. The only food data partitions comprising sufficient data that could support the

assessment of the effect of handling were those of produce and dairy (Table 4). It was found that people who ate unwashed fruits and vegetables, had their odds of infection significantly increased by a factor of 1.572. Hence, the practice of not washing vegetables before consumption represents on its own a risk factor for cryptosporidiosis.

For most of the meta-analytical models reported in Tables 2, 3 and 4, the statistical tests indicated the absence of potential significant publication bias at 5% significance. Exception is observed for partitions related to travel, host-specific in the mixed population, person-to-person transmission, animal contact in children, and composite foods. However, for these five partitions, the spread of data points within the funnel plot does not hint any evidence of a strong publication bias problem (Figure 8). Moreover, the intra-class correlation I^2 indicates low (<25%) to moderate (<50%) heterogeneity (Tables 2, 3 and 4). Remaining between-study heterogeneity (significant p-values below 0.05 for Q or QE) was observed for most of the data partitions.

4. Discussion

This meta-analysis identified foreign travel (pooled OR = 4,216), immunocompromising conditions (pooled OR ranging from 2.721 to 4.507), person-to-person transmission (pooled OR ranging from 1.903 to 3.786), environmental pathways (pooled OR ranging from 1.358 to 1.968 in the mixed population), animal contact (pooled OR ranging from 1.694 to 2.167), and food consumption (pooled OR ranging from 1.533 to 1.934) as risk factors of cryptosporidiosis. For person-to-person, environmental and animal contact pathways, the same risk factors were identified in the mixed population and children. Food exposures were less investigated in children compared to the mixed population. Fewer studies investigated the susceptible population (immunocompromised individuals and elderly) and the pooled OR related to animal, environmental and food exposures were non-significant.

Overall, these meta-analytical results are in line with the epidemiology of *Cryptosporidium* (EFSA BIOHAZ Panel, 2018). Few studies investigated cases caused specifically by *C. parvum* (11*)* or *C. hominis* (1). Although the epidemiology of both *C. parvum* and *C. hominis* could involve indirect transmission routes (water, foods), there are some specificities. *C. hominis*, which infects mainly humans, is transmitted through the fecal-oral pathway and, hence, person-to-person transmission plays a major role in the transmission. On the other hand, the main reservoir of *C. parvum* is ruminants, and, as such, zoonotic transmission could occur through animal contact.

Foreign travel is a known risk factor of cryptosporidiosis (Hagmann et al., 2014). However, due to the lack of information on the countries of travel, it was not possible to identify regions at particular risk (Figure 2).

The host susceptibility risk factors (in particular immunosuppression linked to AIDS) have been established in previous studies (Hunter and Nichols, 2002).

Person-to-person transmission is a known risk factor of cryptosporidiosis. In this meta-analysis, higher pooled OR were obtained for children compared to adults (Figure 3). This might be related to higher exposure due to the lack of hygiene, greater susceptibility, and less immunity. Regarding the person-to-person pathways, contact with an ill person at home (contact in the household), contact in institutions (child /daycare, schools, etc.) and contact during sexual activity were significantly associated with cryptosporidiosis. The lack of personal hygiene (lack of handwashing), identified as a risk factor, can lead to person-to-person transmission.

The meta-analysis confirms the major role of water in the transmission of cryptosporidiosis. Exposure to recreational waters, wastewater (lack of sanitation) and the consumption of untreated drinking water significantly increase the risk of cryptosporidiosis. Many outbreaks of cryptosporidiosis have been associated with the consumption of drinking water (Dalle et al., 2003; Eisenberg et al., 2005; Moreira and Bondelind, 2017), and the ingestion of bathing water in swimming pools or leisure facilities (first cause of outbreak in the United States and the United Kingdom) (Gharpure et al., 2019; Ryan et al., 2017). *Cryptosporidium* is often present in aquatic environments from fecal sources and can be found in a large range of concentrations (1 to several hundred oocysts /L) (Nasser, 2015). *Cryptosporidium* oocysts can bypass common water treatments during occasional failure of the filtration (Lonigro et al., 2006), and are highly resistant to disinfection procedures like chlorination (Erickson and Ortega, 2006).

Contact with farm animals and farm attendance are identified as risk factors, which is supported by described outbreaks. In the US, contact with infected cattle is the second cause of cryptosporidiosis outbreaks, responsible for 15 % outbreaks for the period 2009–2017 (Gharpure et al., 2019). Several outbreaks have also been reported in Europe (Lange et al., 2014; Utsi et al., 2016; Alsmark et al., 2018). Possession of a pet is only significant in children. The role of pets (dogs and cats) in the transmission of cryptosporidiosis is nevertheless not established in the literature (de Lucio et al., 2017; Lucio-Forster et al., 2010).

Among the food-related risk factors, meat was found as a risk factor, which was less expected. Only one outbreak linked to the consumption of raw meat has been reported

(Yoshida et al., 2007). Within the meat category, meat of unspecified origin ("others") is found significant but beef is not a significant risk factor (with only 2 ORs from 2 publications). None of the ORs are significant in each study alone (3 studies from Canada and the United Kingdom), but this factor appears significant by the combination of ORs in the meta-analysis (8 ORs) (Figure 6). This association could reflect fecal contamination of beef carcasses during the slaughter process, as observed with other enteric pathogens (e.g *Salmonella,* or Shigatoxin-producing *E. coli*). Data on the contamination of meat by *Cryptosporidium* are however limited. The prevalence of *Cryptosporidium* spp. in feces and meat samples were investigated by Moriarty et al. (2005): *Cryptosporidium* spp. were isolated from fecal samples (7.3%) but not from carcasses samples. To confirm the plausibility of this association, meat should be explored in specific surveys and investigations of outbreaks and sporadic cases of cryptosporidiosis.

The consumption of dishes prepared outside home and BBQ foods were also found significantly associated with *Cryptosporidium*. This can be linked to poor hygiene practices (e.g. contamination by an infected handler during the preparation of these products).

Unpasteurized milk and dairy products emerged as a risk factor in the meta-analysis. This result is consistent with published outbreaks (Harper et al., 2002; Loury et al., 2019; Rosenthal et al., 2015). *C. parvum* was listed among microbiological hazards potentially transmissible through milk and present in the EU milk-producing animal population (EFSA BIOHAZ Panel, 2015).

However, identification and isolation methods of *Cryptosporidium* are not standardized in dairy products and these products are rarely found contaminated during outbreaks investigations (Loury et al., 2019).

Produce (washed and not washed in the same category) was not identified as a risk factor, but the consumption of poorly washed fruits and vegetables significantly increases ORs. Fresh produce is the main vehicle of foodborne cryptosporidiosis outbreaks (Aberg et al., 2015; England, 2017; Ethelberg et al., 2009; McKerr et al., 2015). Nevertheless, several case-control studies found that the consumption of vegetables is a protective factor against cryptosporidiosis (Goh et al., 2004; Nic Lochlainn et al., 2019; Roy et al., 2004). Roy et al. (2004) explained this effect by the acquisition of protective immunity following repeated exposure to low doses of oocysts on contaminated vegetables as observed in waterborne outbreaks (Hunter, 2000). Produce (vegetables) should be better studied by taking into account the type of vegetable (more exposed or not to irrigation of contaminated waters, such as lettuce) and the type of preparation (washed or not).

Beverages (including cider/bottled water/ice) were not identified as a risk factor in the meta-analysis. Cider was investigated in one study and was found non-significant (Roy et al., 2004). Apple cider/juice has been responsible for two outbreaks in the USA (Blackburn et al., 2006; Millard et al., 1994) and recently in Norway (Robertson et al., 2019). Recommendations have been made on grazing animals in orchards and washing fruits. Shellfish are considered as potential vehicles of *Cryptosporidium* but were not investigated in the included studies. Although shellfish have been found contaminated with *Cryptosporidium* oocysts in several surveys (Giangaspero et al., 2014; Gomez-Bautista et al., 2000; Gomez-Couso et al., 2006; Robertson and Gjerde, 2008), no outbreaks have been reported to date. The role of shellfish in *Cryptosporidium* infections should be investigated in future case-control studies.

Our results are comparable to the meta-analysis conducted by Bouzid et al. (2018) who reported diarrhea in the household, animal contact, lack of toilet facility and overcrowded conditions as risk factors for cryptosporidiosis in low and middle-income countries based on 11 studies. Food exposures were not investigated in the included studies and poor drinking water was not found significant. These differences may be related to the analysis strategy of Bouzid et al. (2018) as only studies reporting at least four relevant risk factors were included in their meta-analysis.

5. Conclusion

In summary, this meta-analysis confirmed known risk factors of cryptosporidiosis linked to anthroponotic and zoonotic pathways of transmission: contact with infected humans, waterborne transmission, contact with animals and food consumption. Except for meat, the identified vehicles are all consistent with described outbreaks.

Future case-control studies of sporadic infections should better explore the role of dairy, shellfish, meat, and vegetables, including washing/cooking and hygiene practices. These risk factors should also be included in questionnaires used for outbreak investigations. Moreover, the development of sensitive methods (based on molecular assays) for detection and isolation of *Cryptosporidium* oocysts in these different matrices is necessary to link cases to food items (Rousseau et al., 2018). Susceptible populations, such as children, elderly or immunosuppressed people could be better addressed, due to the severity of cases in those populations. The immunity should be taken into account to reduce misclassification in case-control studies (Hunter, 2000). It may be interesting to consider serology, in addition to criteria related to symptoms, and parasite excretion. In order to improve the detection of

cases, biological diagnosis of persistent diarrhea should specify *Cryptosporidiu*m research (Loury et al, 2019).

Lastly, subtyping of human isolates can provide insights into the epidemiology of cryptosporidiosis, allowing the identification of risk factors specific to species or subtypes.

Appendices: Supplementary material

Appendix 1: References of the 57 primary studies

Appendix 2: Non-significant results on the main risk factors

Data statement

Acknowledgments

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Figures

- Figure 1: Flow chart of literature search for case-control or cohort studies of human cryptosporidiosis
- Figure 2: Forest plot of the association of cryptosporidiosis with travel abroad
- Figure 3: Forest plot of the association of cryptosporidiosis with person-to-person transmission in children
- Figure 4: Forest plot of the association of cryptosporidiosis with contact with farm animals in the mixed population
- Figure 5: Forest plot of the association of cryptosporidiosis with contact with recreational waters in the mixed population

Tables

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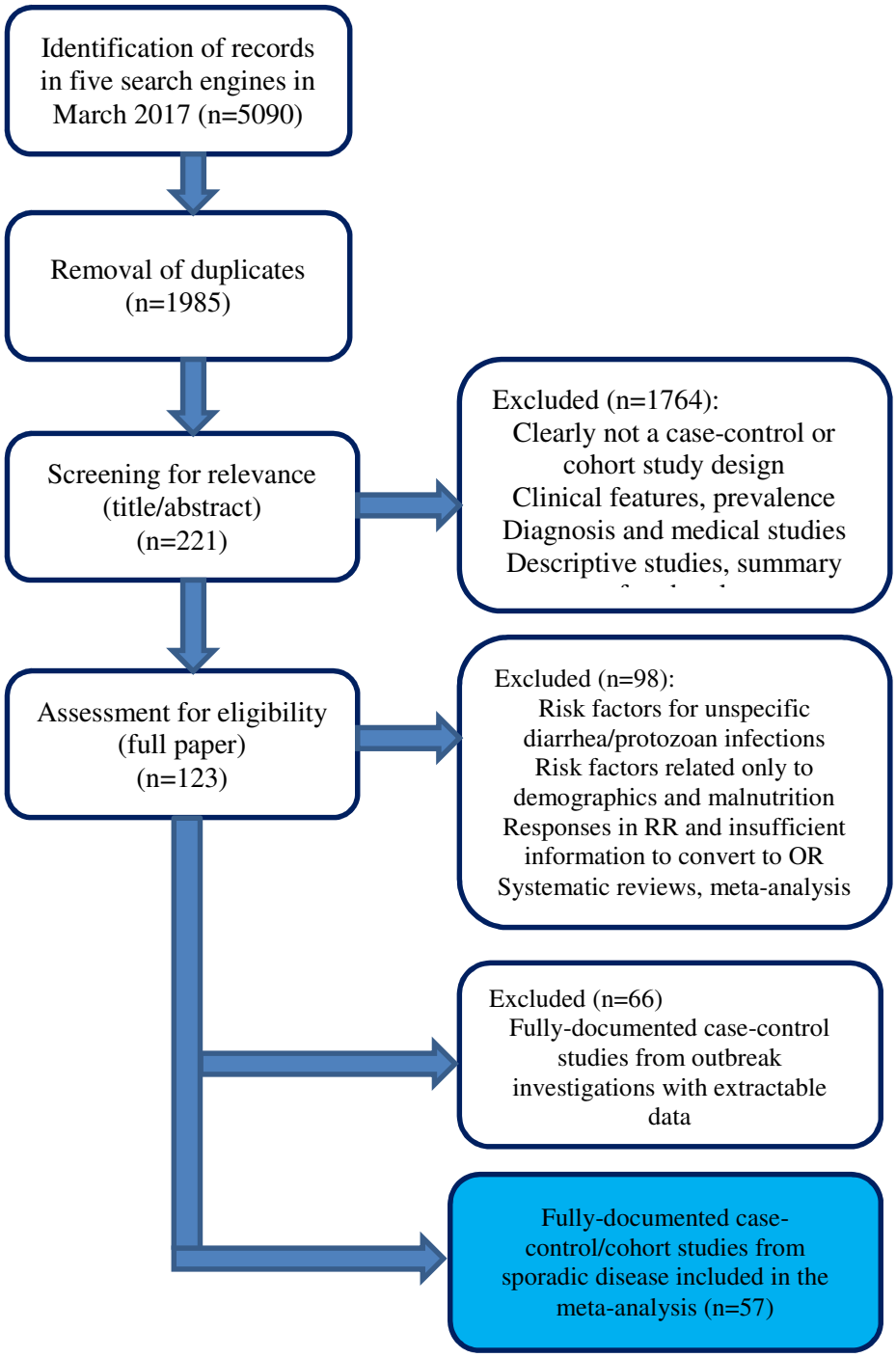


Figure 1. Flow chart of literature search for case-control or cohort studies of human cryptosporidiosis

Figure 2. Forest plot of the association of cryptosporidiosis with travel abroad transmission in all populations (* adjusted OR as described in Gonzales-Barron et al. (2019) n=14

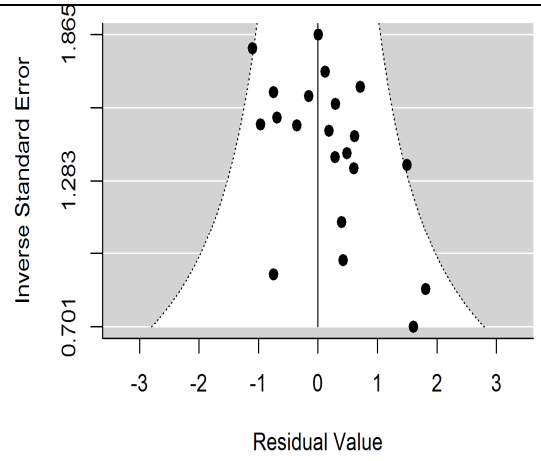
Figure 3. Forest plot of the association of cryptosporidiosis with person-to-person transmission in children (* adjusted OR as described in Gonzales-Barron et al. (2019) n=7

Figure 4. Forest plot of the association of cryptosporidiosis with contact with farm animals in the mixed population (* adjusted OR as described in Gonzales-Barron et al. (2019) n=41

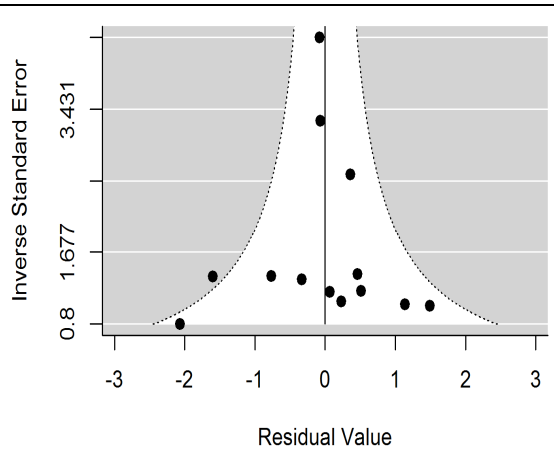
Figure 5. Forest plot of the association of cryptosporidiosis with contact with recreational waters in the mixed population (* adjusted OR as described in Gonzales-Barron et al. (2019) n=65

Figure 6. Forest plot of the association of cryptosporidiosis with meat consumption in the mixed population (* adjusted OR as described in Gonzales-Barron et al. (2019) n=9

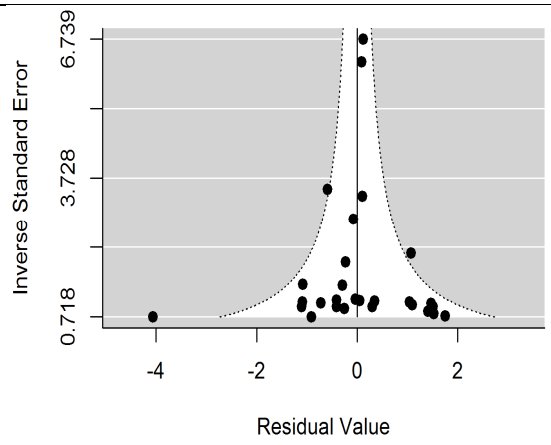
Figure 7. Forest plot of the association of cryptosporidiosis with dairy consumption in the mixed population (* adjusted OR as described in Gonzales-Barron et al. (2019) n=10



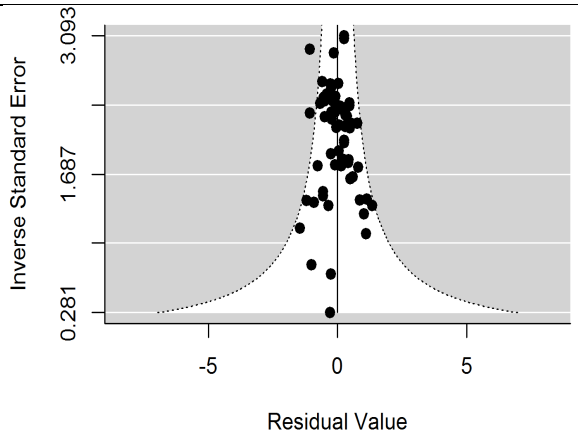
Travel in Mixed population



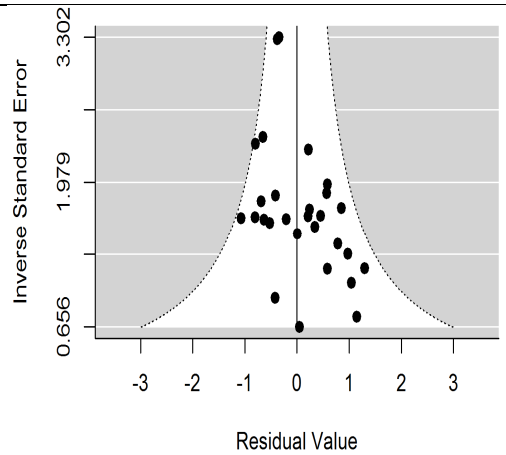
Host-specific in Mixed population



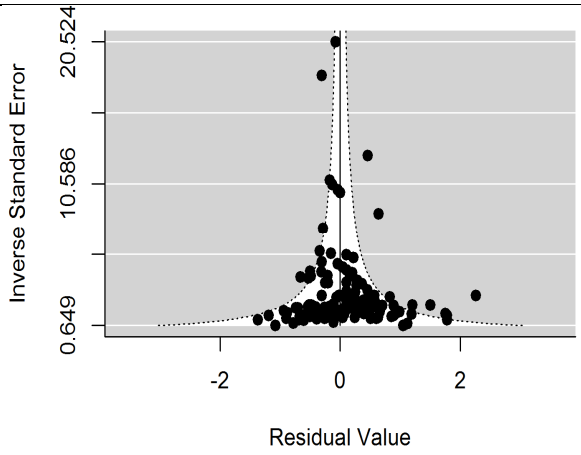
Host-specific in Children



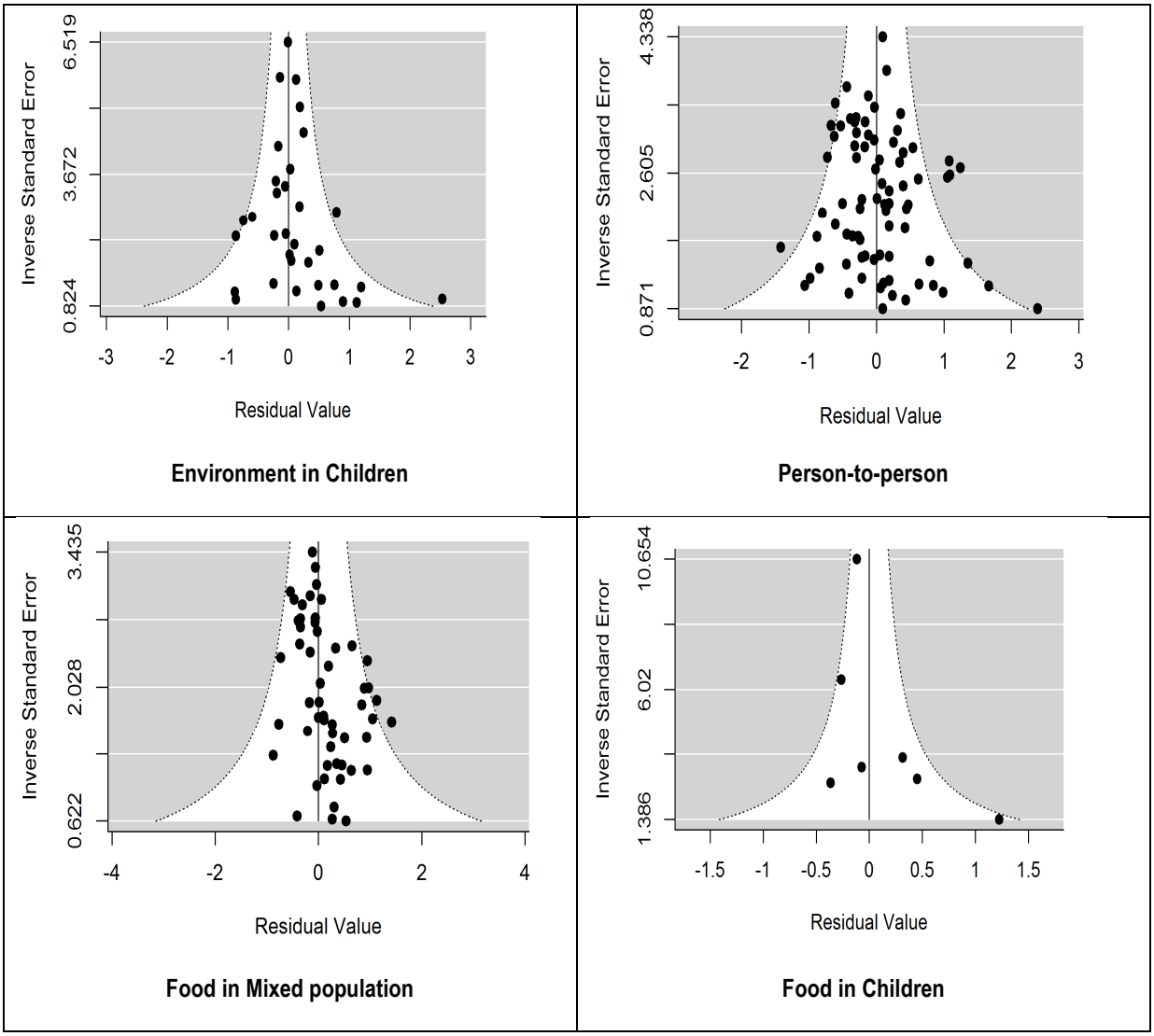
Animal contact in Mixed population



Animal contact in Children



Environment in Mixed population



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694 **Figure 8: Funnel plots of studies investigating categorized risk factors (travel, host-**
695 **specific, environment, animal contact, person-to-person and food)**

696

697 **Table 1. Characteristics of primary studies investigating risk factors for acquiring**
698 **sporadic cryptosporidiosis included in the meta-analysis**
699

StudyID	Country	Study period	Population	Design	Analysis &model	# ill/ non-ill	Quality
Abdel-Messih et al., 2000	Egypt	May 2000 - May 2002	Children	Unmatched	Uni -Chi Uni-UL	90 ill 791 non-ill	Good
Al-Dabbagh et al., 2010	Iraq	June 2003– Oct 2003	Children	Matched	Uni –Chi Multi-UL	100 ill 100 non-ill	Good
Al-Shibani et al., 2009	Egypt	2009	Mixed	Unmatched	Uni- Chi	70 ill 222 non-ill	Good
Aragón et.al., 2003	USA	May 1996- Sep 1998	Susceptible	Matched	Uni –CL Multi-CL	49 ill 99 non-ill	Good
Bhattacharya et al., 1997	Bangladesh	1991-1994	Children	Unmatched	Uni –Chi Multi-UL	68 ill 204 non-ill	Good
Bouratbine et al., 1998	Tunisia	1997	Children	Unmatched	Uni –Chi	12 ill 120 non-ill	Good
Chacín-Bonilla et al., 2008	Venezuela	2017	Mixed	Unmatched	Multi-UL	67 ill 448 non-ill	Good
Chen et al., 2017	China	2011-2012	Children	Unmatched	Uni –Chi	40 ill 531 non-ill	Good
Cohen et al., 2008	USA	1992-2002	Children Adult Susceptible	Unmatched	Uni-UL Multi-UL	Not stated	Good
Cruz et al., 1988	Guatemala	July 1985- June 1986	Children	Unmatched	Uni –Chi	19 ill 110 non-ill	Good
Egger et al., 1990	Switzerland	June-Sep 1988	Children	Matched	Uni- Chi	19 ill 38 non-ill	Good
El-Shabrawi et al., 2015	Egypt	Sep 2007- Sep 2009	Children	Matched	Uni- Chi	14 ill 236 non-ill	Good
Firdu et al., 2014	Ethiopia	Feb-Aug 2011	Children	Unmatched	Uni –Chi	11 ill 18 non-ill	Poor
Fournet et al., 2013	Netherlands	Aug 2012	Mixed	Unmatched	Uni-Chi Multi-UL	82 ill 125 non-ill	Good
Gallaher et al., 1989	Mexico	July-Oct 1986	Mixed	Matched	Uni-MH	24 ill 46 non-ill	Good
Girotto et al., 2013	Brazil	Dec 2009- Oct 2010	Susceptible	Unmatched	Uni –Chi	3 ill 290 non-ill	Good
Glaser et al., 1998	USA	Apr 1992- Nov 1994	Susceptible	Unmatched	Uni –Chi	48 ill 99 non-ill	Good
Goh et al., 2004	UK	Jan 1998-Feb 2000	Mixed	Unmatched	Uni-Chi Multi-UL	152 ill 466 non-ill	Good
Hellard et al., 2003	Australia	Oct 1998- Aug 2000	Mixed	Unmatched	Uni –Chi	10 ill 24 non-ill	Good
Helmy et al., 2015	Egypt	Apr-June 2011	Children	Unmatched	Uni –Chi	81 ill 84 non-ill	Good
Hunter et al., 2004	UK	Feb 2001- May 2002	Mixed	Unmatched	Uni-Chi Multi-UL	427 ill 400 non-ill 261 ill 351 non-ill	Good
Izadi et al., 2014	Iran	Sep 2009- Mar 2010	Mixed	Unmatched	Uni-Chi Multi-UL	28 ill 394 non-ill	Good
Izadi et al., 2012	Iran	Nov 2008- Mar 2009	Susceptible	Unmatched	Uni-Chi Multi-UL	11 ill 172 non-ill	Good
Khalakdina et al., 2003	USA	July 1999- July 2001	Mixed	Matched	Uni-CL Multi-CL	26 ill 62 non-ill	Good
Khan et al., 2004	Bangladesh	May 2001- Aug 2002	Children	Unmatched	Uni –Chi	46 ill 46 non-ill	Good

Kutima et al., 2015	Kenya	Jan 2011-June 2013	Children	Unmatched	Uni –Chi	36 ill 676 non-ill	Good
Lake et al., 2007	UK	2000-2004	Mixed	Matched	Multi –CL	3368 ill 3368non-ill	Good
Mahdi and Ali, 2002	Iraq	2002	Mixed	Unmatched	Uni –Chi	5 ill 230 non-ill	Good
Manabe et al., 1998	USA	July 1989-1997	Susceptible	Unmatched	Uni –Chi	68 ill 129 non-ill	Good
Marder, 2012	USA	2003-2010	Mixed	Unmatched	Uni –UL	6534 ill 30890 non-ill	Poor
Mbae et al., 2013	Kenya	Jan 2010-Dec 2011	Children	Unmatched	Uni-Chi Multi-UL	187 ill 1925 non-ill	Good
Mitra et al., 2016	India	2016	Mixed	Unmatched	Uni –Chi	59 ill 233 non-ill	Good
Mølbak et al., 1994	Guinea-Bissau	1992	Children	Matched	Multi-CL	125 ill 125 non-ill	Good
Mooji et al., 2015	Netherlands	2013-2015	Mixed	Unmatched	Uni-UL Multi-UL	312 ill 587 non-ill	Good
Moore et al., 2016	Cambodia	Apr-June 2012	Children	Unmatched	Uni-Chi Multi-UL	38 ill 460 non-ill	Good
Morse et al., 2008	Malawi	Jan 2001-Dec 2002	Children	Unmatched	Uni-Chi Multi-UL	24 ill 72 non-ill	Good
Nassar et al., 2017	Nigeria	July-Dec 2014	Children	Unmatched	Uni-Chi	88 ill 100 non-ill	Good
Nchito et al., 1998	Zambia	Nov 1995-Mar 1996	Children	Unmatched	Uni-Chi Uni-MH	37 ill 179 non-ill	Good
Ng et al., 2012	Australia	July-Aug 2010	Mixed	Unmatched	Uni-Chi	15 ill 48 non-ill	Good
Nimri and Hijazi, 1994	Jordan	July 1992-Sep 1993	Children	Matched	Uni-Chi	18 ill 18 non-ill	Good
Osman et al., 2016	Lebanon	Jan 2013	Children	Unmatched	Uni-UL	26 ill 223 non-ill	Good
Pereira et al., 2002	Brazil	Aug 1998-May 1999	Children	Unmatched	Uni-UL	64 ill 380 non-ill	Good
Pintar et al., 2009	Canada	Apr 2005-Dec 2007	Mixed	Unmatched	Uni-Chi Multi-UL	36 ill 801 non-ill	Poor
Ravel et al., 2013	Canada	June 2005-May 2009	Mixed	Unmatched	Uni-Chi	51 ill 54 non-ill	Poor
Redlinger et al., 2002	Mexico	Aug 1999-Mar 2000	Mixed	Unmatched	Uni-Chi	298 ill 345 non-ill	Poor
Robertson et al., 2002	Australia	June 1998-May 2001	Children Mixed	Matched	Uni-CL Uni-CL Multi-CL	64 ill 262 non-ill 201 ill 795 non-ill	Good
Roy et al., 2004	USA	1999-2001	Mixed	Matched	Uni-MH Multi-CL	267 ill 464 non-ill 233 ill 467 non-ill	Good
Sarkar et al., 2014	India	2008-2013	Children	Unmatched	Uni-UL Multi-UL	411 ill 180 non-ill 113 ill 51 non-ill	Good
Solorzano-Santos et al., 2000	Mexico	2000	Children	Unmatched	Uni-Chi Multi-UL	10 ill 122 non-ill	Good
Sorvillo et al., 1994	USA	1983-1990	Susceptible	Unmatched	Uni-MH	125 ill 2354 non-ill	Good
Srisuphanunt et al., 2008	Thailand	2007	Susceptible	Unmatched	Uni-Chi	23 ill 120 non-ill	Good
Tellevik et al., 2015	Tanzania	Aug 2010-July 2011	Children	Unmatched	Uni-Chi Multi-UL	23 ill 397 non-ill	Good

Tumwine et al., 2003	Uganda	Nov 1999-Jan 2001	Susceptible	Matched	Uni-Chi	488 ill 1291 non-ill	Good
Valderrama et al., 2009	USA	Aug-Sep 2007	Mixed	Matched	Uni-CL Multi-CL	47 ill 92 non-ill 45 ill 89 non-ill	Good
Velasco et al., 2011	Colombia	Feb-Apr 2009	Susceptible	Unmatched	Uni-Chi Multi-UL	38 ill 93 non-ill	Good
Wilson et al., 2008	NewZealand	2006	Mixed	Unmatched	Uni-Chi	534 ill 5395 non-ill	Poor
Yang et al., 2017	China	Oct-Nov 2014	Mixed	Unmatched	Uni-Chi Multi-UL	73 ill 543 non-ill 73 ill 542 non-ill	Good

702 **Table 2. Results of the meta-analysis on the main risk factors**

Population	Geographical area	Risk factor	Pooled OR [95% CI]	N/n*	p-value of risk factor	Publication bias p-value	Points removed **	Heterogeneity analysis***
Travel								
All	**All**	Abroad	4.216 [2.529 - 7.029]	9/14	<.0001	0.0408	0	τ^2=0.284 QE(df = 19) = 73.419, p-val < .0001 S^2=0.656; I^2=30.205%
Host specific								
Mixed(y)	**All**	Immunocompromising conditions	4.507 [2.168 - 9.367]	6/10	<.0001	0.022	0	τ^2=0.5591 QE(df = 11) = 42.355, p-val < .0001 S^2=0.973 ; I^2= 36.5028
		Other medical conditions	2.392 [1.588 - 3.604]	2/3	<.0001			
Children	**All**	Immunocompromising conditions	2.721 [2.147 - 3.448]	4/7	<.0001	0.366	0	τ^2=0.897 QE(df = 25) = 102.641, p-val < .0001 S^2=1.39902 I^2= 39.06
Transmission Person to person by population								
Mixed	**All**		2.489 [2.033 - 3.049]	12/69	<.0001	<.0001	0	τ^2=0.2578 QE(df = 80) = 199.431, p-val < .0001 S2=0.393 I2=39.62%
Children			3.786 [1.989 - 7.205]	5/7	<.0001			
Susceptible			1.903 [1.170 - 3.095]	5/7	0.010			
Transmission Person to person by type of contact								
All	**All**	Contact in the community	3.339 [2.623 - 4.243]	6/14	<.0001	0.304	1	τ^2= 0.0485 QE(df = 65) = 167.161, p-val < .0001 S^2=0.315 I^2=13.35%
		Sexual transmission	2.350 [1.439 - 3.837]	3/11	<.0001			
		Contact in the household	2.191 [1.771 - 2.711]	9/43	0.001			
Personal Hygiene								
All	**All**	**All**	1.736 [1.286 - 2.343]	4/4	0.0003	0.453	0	τ^2=0 Q(df = 3) = 4.2604, p-val = 0.2347 S^2=0.189 I^2=0
Animal contact								
Mixed	**All**	Farm animals	2.167 [1.703 - 2.758]	13/41	<.0001	0.698	3	τ^2=0.2953 QE(df = 64) = 224.108, p-val < .0001 ; S^2=0.336 ; I^2=46.772
Children	**All**	Farm animals	1.968 [1.284 - 3.018]	9/15	0.002	<.0001	0	τ^2=0.359 QE(df = 28) = 59.869, p-val = 0.0004 S^2=0.458 I^2= 43.967
		Pets	1.694 [1.297 - 2.212]	8/15	<.0001			
Environment								
Mixed	**All**	Farm environment	1.794 [1.444 - 2.230]	5/18	<.0001	0.555	**2**	τ^2=0.601 QE(df = 143) = 1534.2984, p-val < .0001 ;S2=0.351 I^2=63.119
		Untreated drinking Water	1.358 [1.249 - 1.475]	14/46	<.0001			
		Recreational water	1.968 [1.475 - 2.625]	14/65	<.0001			
		Wastewater	1.697 [1.127 - 2.555]	5/8	0.011			

		Daycare attendance	1.539 [1.429 - 1.659]	3/5	<.0001			
Children	**Oceania removed (2 OR excluded)**	Farm environment	1.802 [1.194 - 2.719]	3/3	0.005	0.079	0	τ^2=0.0182 QE(df = 28) = 33.467, p-val = 0.219 S^2=0.464 I^2=3.774
		Daycare attendance	1.742 [1.031 - 2.945]	3/3	0.038			
		Untreated drinking Water	1.367 [1.092 - 1.712]	9/19	0.006			
		Recreational water	4.114 [1.579 - 10.72]	2/2	0.004			
Food								
Mixed	**All**	Dairy	1.533 [1.009 - 2.329]	4/10	0.045	0.248	0	τ^2=0.2602 QE(df = 50) = 159.0378, p-val < .0001 S^2=0.26 ; I2=49.99
		Meat	1.934 [1.236 - 3.024]	4/9	0.004			
Children	**All**	Composite	1.532 [1.072 - 2.189]	2/2	0.019	0.993	0	τ^2=0 QE(df = 4) = 5.9980, p-val = 0.1993 S^2=0.304 ; I^2=0

*N/n Number of studies/number of OR;** points removed by sensitivity analysis, all results are given after removing data concerned; ***Between-study variability (τ^2), test for residual heterogeneity (QE), variance of residuals (s^2), intra-class correlation (I^2). ****Immunosuppressed or HIV positive; (y): year is significant (before/after 2000) in this model and the estimates are taking this effect into account

Table 3. Results of the meta-analysis on disaggregated risk factors

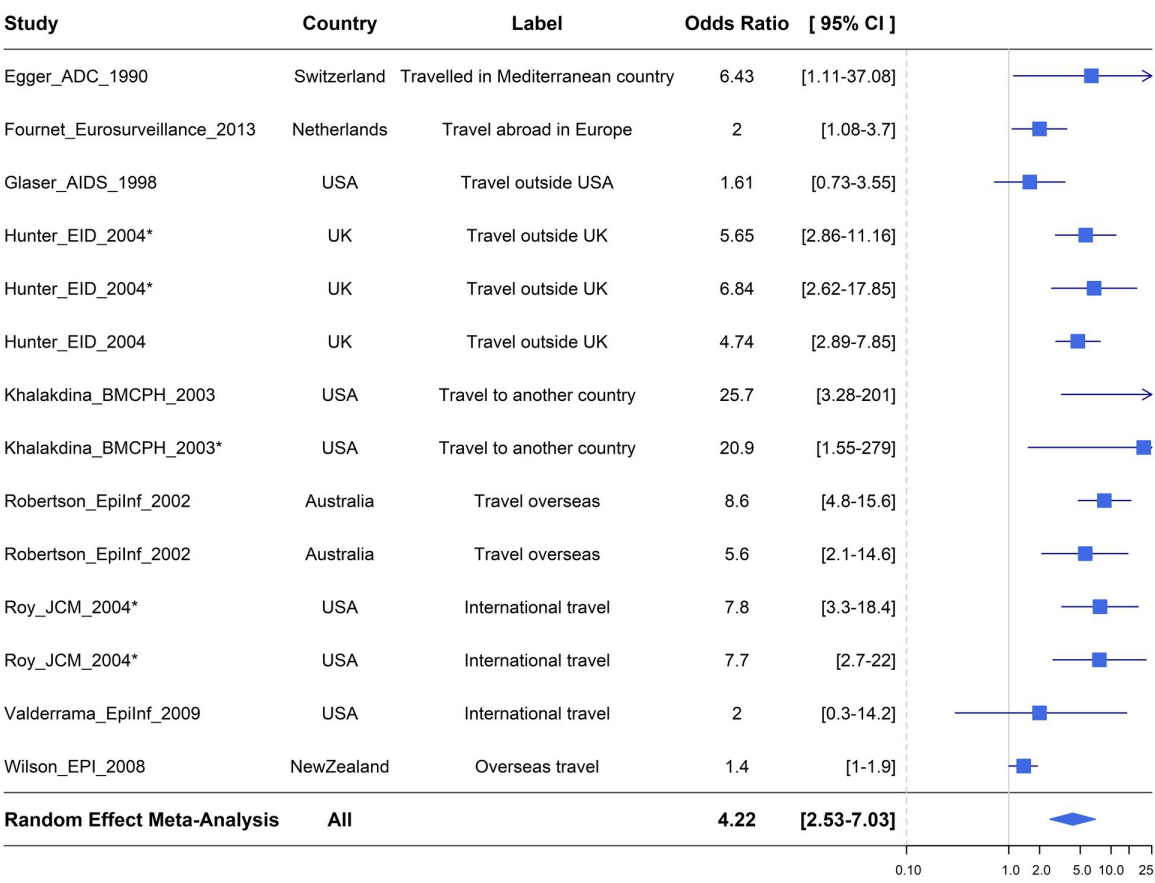
Risk Factor	Population	Geographical area	Risk factor precise	Pooled OR [95% CI]	N/n*	p-value of risk factor	Publication bias p-value	Points removed **	Heterogeneity analysis***
Meat	Mixed & Susceptible	All	Others****	1.991 [1.288 - 3.080]	3/8	0.002	0.890	0	τ2=0 QE(df = 8) = 4.5068, p-val = 0.809 S^2=0.243 I^2=0
Dairy	Mixed & Children	All	Milk	1.509 [1.071 - 2.125]	6/8	0.019	0.647	0	τ^2=0 QE(df = 10) = 8.5624, p-val = 0.574 S^2=0.0.205 I^2=0
Composite	Mixed & Children	All	Dishes	1.717 [1.220 - 2.416]	6/17	0.002	0.015	0	τ^2=0.142 QE(df = 18) = 126.1028, p-val < .0001 s2=0.330 I^2=30.085
BBQ	All	All	BBQ	2.005 [1.624 - 2.476]	2/4	<.0001	0.383	0	τ^2=0 Q(df = 3) = 26.214, p-val < .0001 S^2=0.315 I^2=0

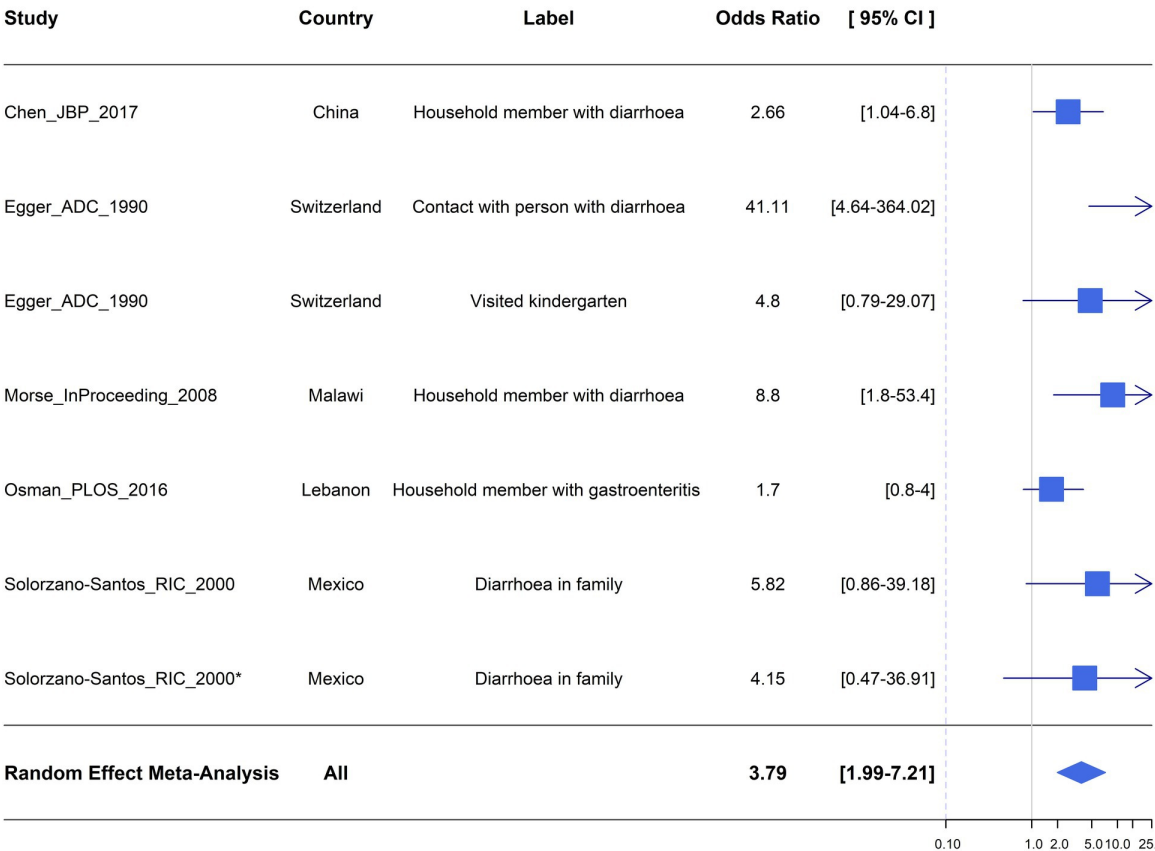
*N/n Number of studies/number of OR;** points removed by sensitivity analysis, all results are given after removing data concerned; ***Between-study variability (τ^2), test for residual heterogeneity (QE), variance of residuals (s^2), intra-class correlation (I^2); **** Meats of non-specified origin

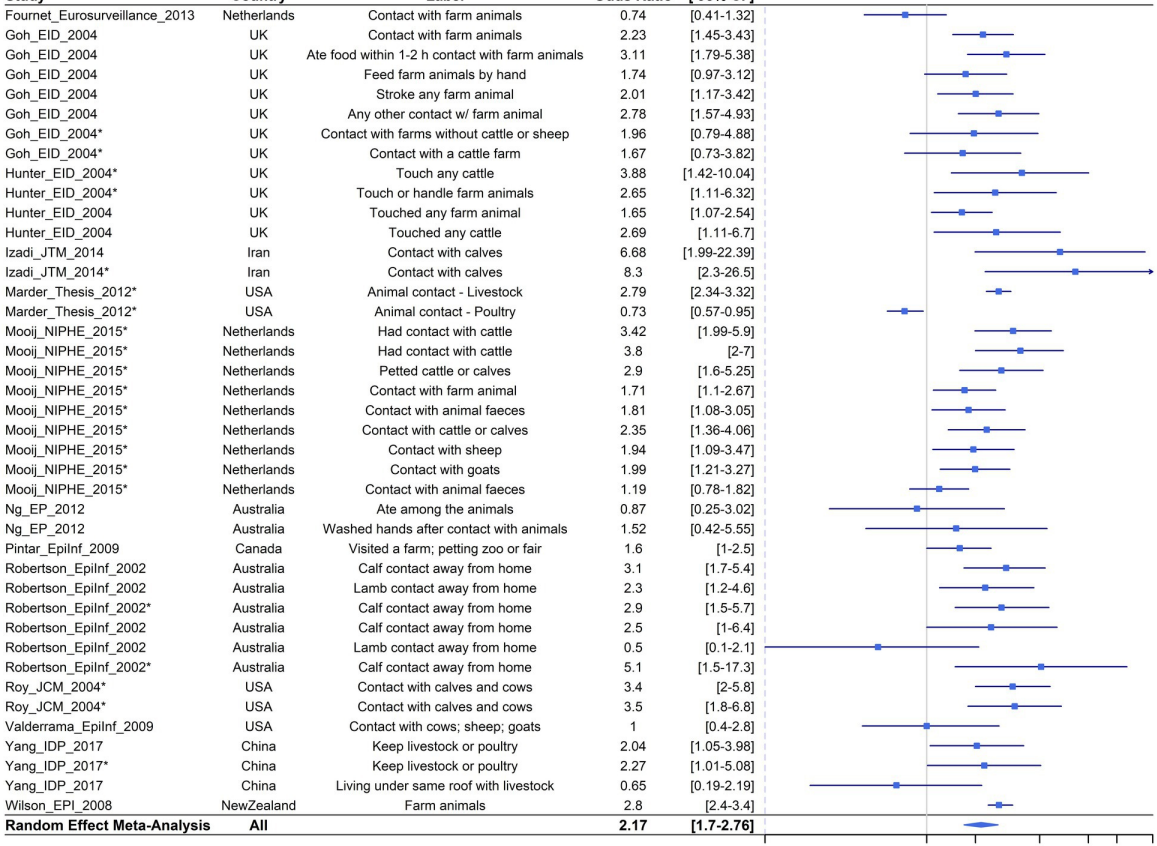
Table 4. Effect of handling on the pooled OR for produce

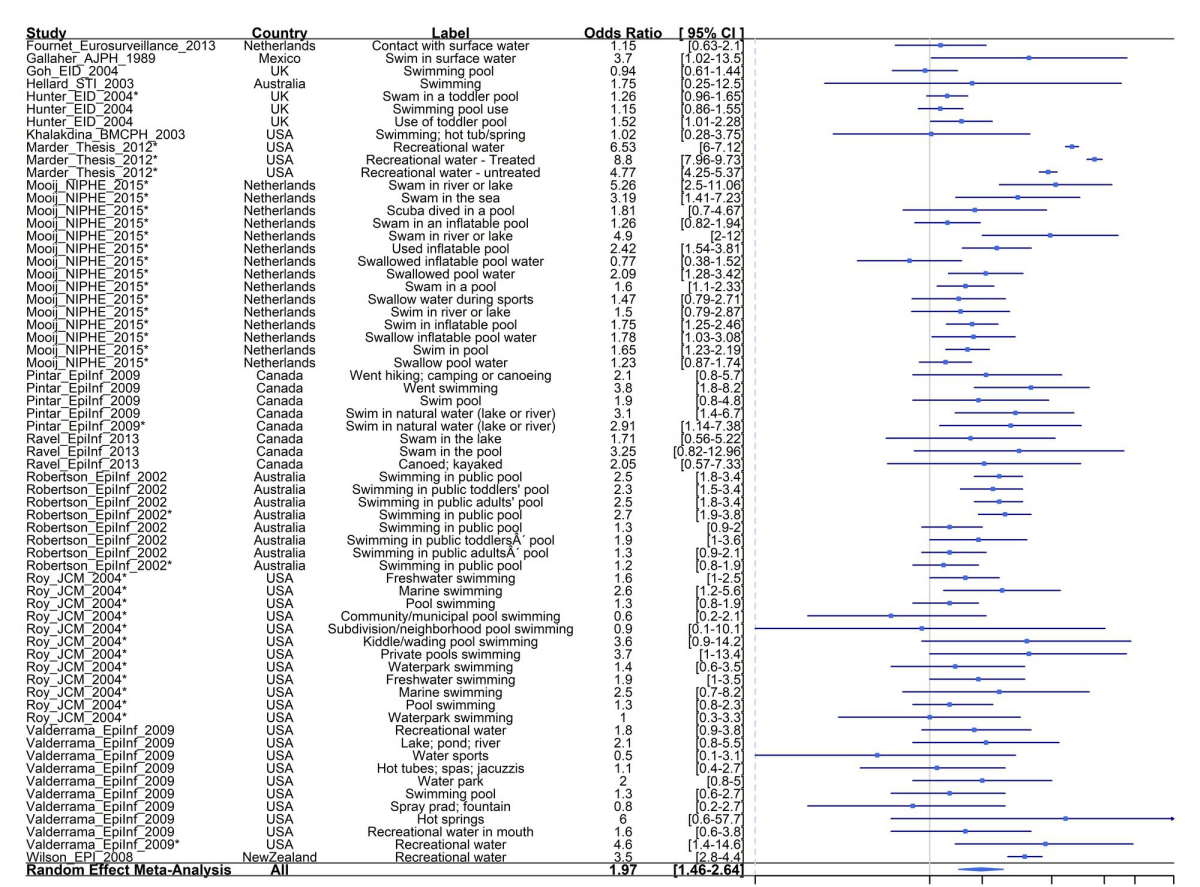
Risk Factor	Risk factor precise	Pooled OR [IC95%]	N/n*	p-value of risk factor	OR ratios [CI95%]	Points removed **	Publication bias p-value	Heterogeneity analysis**
Produce	**Unwashed**	1.159 [0.615 - 2.185]	3/4	0.039	1.572 [1.021 - 2.419]	0	0.236	$\tau 2=0$ QE(df = 9) = 9.7450, p-val = 0.3715 $S^2=0.151$ $I^2=0$
	Base	0.737 [0.602 - 0.903]	6/7	0.003				

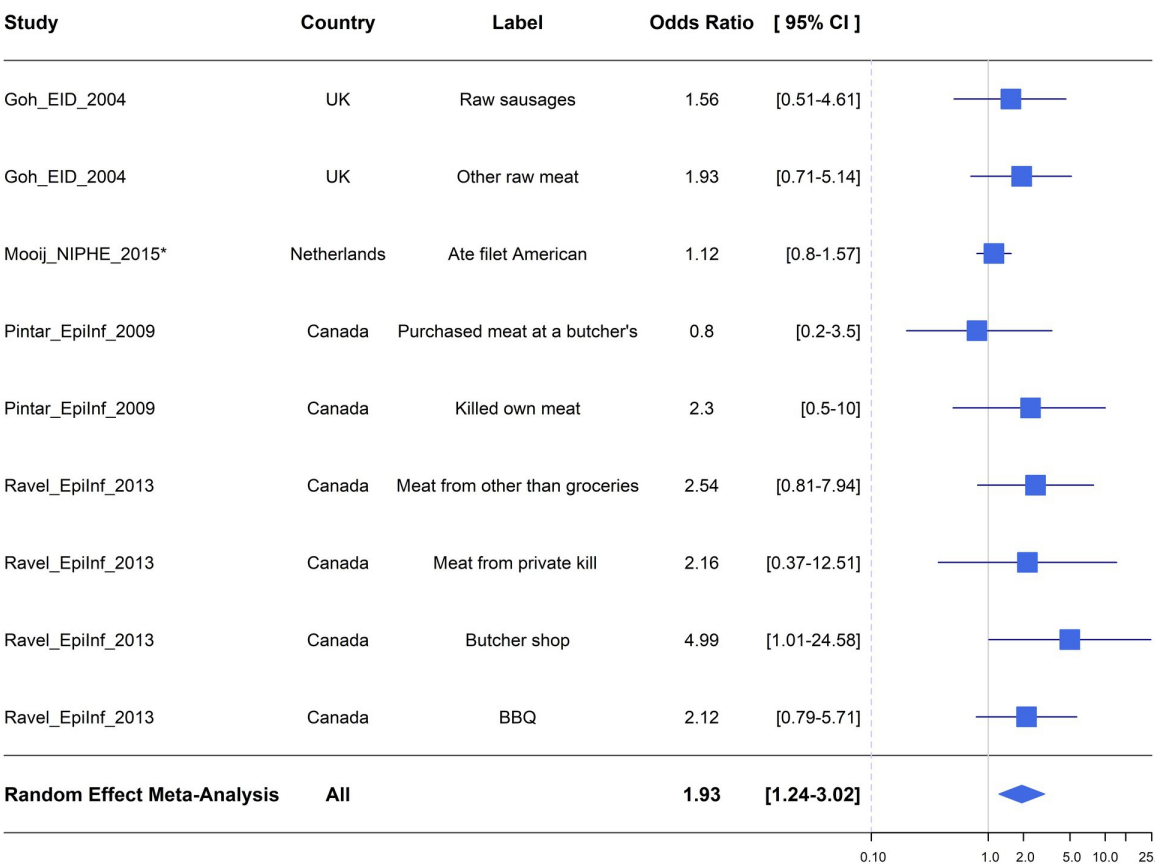
*N/n Number of studies/number of OR;** points removed by sensitivity analysis, all results are given after removing data concerned; ***Between-study variability (τ^2), test for residual heterogeneity (QE), variance of residuals (s^2), intra-class correlation (I^2).

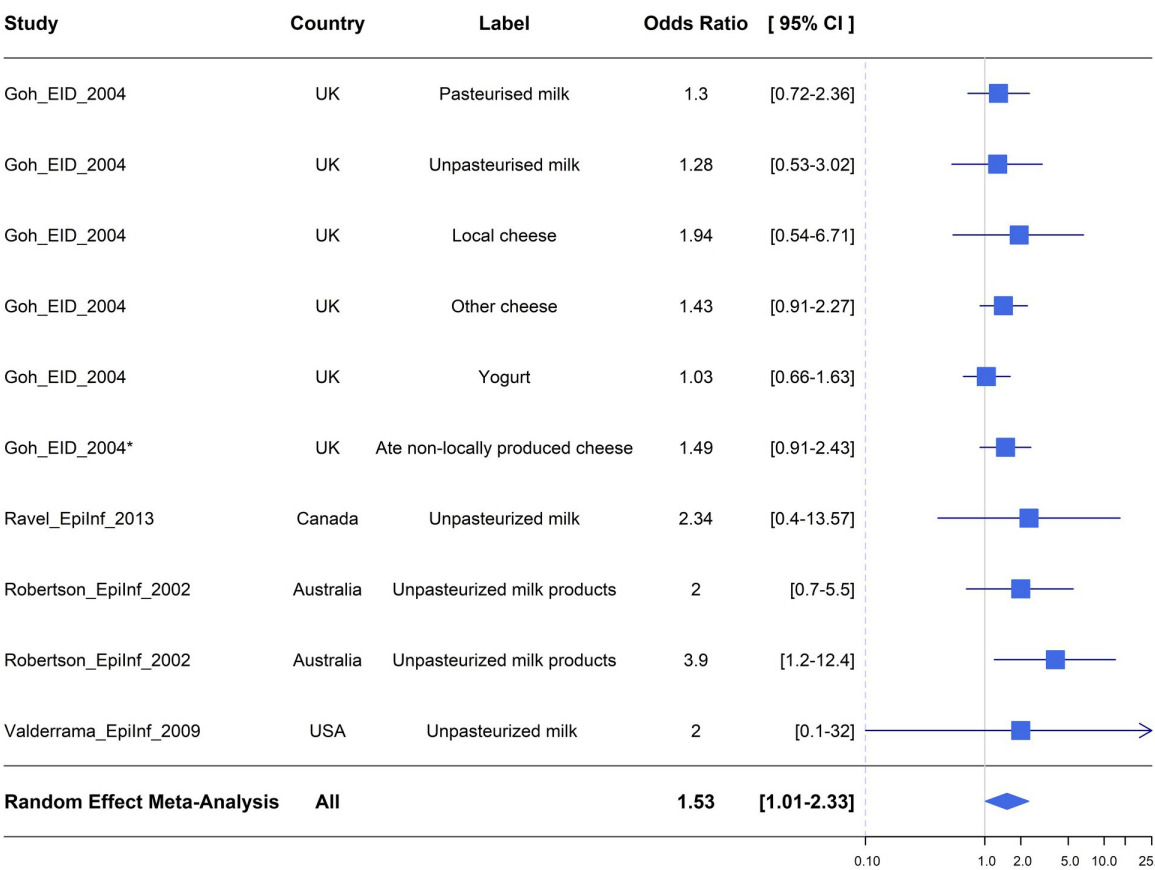

Study
Country
Label
Odds Ratio
[95% CI]
Egger_ADC_1990 Switzerland Travelled in Mediterranean country 6.43 [1.11-37.08]
Fournet_Eurosurveillance_2013 Netherlands Travel abroad in Europe 2 [1.08-3.7]
Glaser_AIDS_1998 USA Travel outside USA 1.61 [0.73-3.55]
Hunter_EID_2004* UK Travel outside UK 5.65 [2.86-11.16]
Hunter_EID_2004* UK Travel outside UK 6.84 [2.62-17.85]
Hunter_EID_2004 UK Travel outside UK 4.74 [2.89-7.85]
Khalakdina_BMCPH_2003 USA Travel to another country 25.7 [3.28-201]
Khalakdina_BMCPH_2003* USA Travel to another country 20.9 [1.55-279]
Robertson_EpiInf_2002 Australia Travel overseas 8.6 [4.8-15.6]
Robertson_EpiInf_2002 Australia Travel overseas 5.6 [2.1-14.6]
Roy_JCM_2004* USA International travel 7.8 [3.3-18.4]
Roy_JCM_2004* USA International travel 7.7 [2.7-22]
Valderrama_EpiInf_2009 USA International travel 2 [0.3-14.2]
Wilson_EPI_2008 NewZealand Overseas travel 1.4 [1-1.9]
Random Effect Meta-Analysis All 4.22 [2.53-7.03]
0.10
1.0
2.0
5.0
10.0
25.0


Study
Country
Label
Odds Ratio
[95% CI]
Chen_JBP_2017
China
Household member with diarrhoea
2.66
[1.04-6.8]
Egger_ADC_1990
Switzerland
Contact with person with diarrhoea
41.11
[4.64-364.02]
Egger_ADC_1990
Switzerland
Visited kindergarten
4.8
[0.79-29.07]
Morse_InProceeding_2008
Malawi
Household member with diarrhoea
8.8
[1.8-53.4]
Osman_PLOS_2016
Lebanon
Household member with gastroenteritis
1.7
[0.8-4]
Solorzano-Santos_RIC_2000
Mexico
Diarrhoea in family
5.82
[0.86-39.18]
Solorzano-Santos_RIC_2000*
Mexico
Diarrhoea in family
4.15
[0.47-36.91]
Random Effect Meta-Analysis
All
3.79
[1.99-7.21]
0.10
1.0
2.0
5.0
10.0
25.0


Study
Country
Label
Odds Ratio
[95% CI]
Fournet_Eurosurveillance_2013 Netherlands Contact with farm animals 0.74 [0.41-1.32]
Goh_EID_2004 UK Contact with farm animals 2.23 [1.45-3.43]
Goh_EID_2004 UK Ate food within 1-2 h contact with farm animals 3.11 [1.79-5.38]
Goh_EID_2004 UK Feed farm animals by hand 1.74 [0.97-3.12]
Goh_EID_2004 UK Stroke any farm animal 2.01 [1.17-3.42]
Goh_EID_2004 UK Any other contact w/ farm animal 2.78 [1.57-4.93]
Goh_EID_2004* UK Contact with farms without cattle or sheep 1.96 [0.79-4.88]
Goh_EID_2004* UK Contact with a cattle farm 1.67 [0.73-3.82]
Hunter_EID_2004* UK Touch any cattle 3.88 [1.42-10.04]
Hunter_EID_2004* UK Touch or handle farm animals 2.65 [1.11-6.32]
Hunter_EID_2004 UK Touched any farm animal 1.65 [1.07-2.54]
Hunter_EID_2004 UK Touched any cattle 2.69 [1.11-6.7]
Izadi_JTM_2014 Iran Contact with calves 6.68 [1.99-22.39]
Izadi_JTM_2014* Iran Contact with calves 8.3 [2.3-26.5]
Marder_Thesis_2012* USA Animal contact - Livestock 2.79 [2.34-3.32]
Marder_Thesis_2012* USA Animal contact - Poultry 0.73 [0.57-0.95]
Mooij_NIPHE_2015* Netherlands Had contact with cattle 3.42 [1.99-5.9]
Mooij_NIPHE_2015* Netherlands Had contact with cattle 3.8 [2-7]
Mooij_NIPHE_2015* Netherlands Petted cattle or calves 2.9 [1.6-5.25]
Mooij_NIPHE_2015* Netherlands Contact with farm animal 1.71 [1.1-2.67]
Mooij_NIPHE_2015* Netherlands Contact with animal faeces 1.81 [1.08-3.05]
Mooij_NIPHE_2015* Netherlands Contact with cattle or calves 2.35 [1.36-4.06]
Mooij_NIPHE_2015* Netherlands Contact with sheep 1.94 [1.09-3.47]
Mooij_NIPHE_2015* Netherlands Contact with goats 1.99 [1.21-3.27]
Mooij_NIPHE_2015* Netherlands Contact with animal faeces 1.19 [0.78-1.82]
Ng_EP_2012 Australia Ate among the animals 0.87 [0.25-3.02]
Ng_EP_2012 Australia Washed hands after contact with animals 1.52 [0.42-5.55]
Pintar_EpiInf_2009 Canada Visited a farm; petting zoo or fair 1.6 [1-2.5]
Robertson_EpiInf_2002 Australia Calf contact away from home 3.1 [1.7-5.4]
Robertson_EpiInf_2002 Australia Lamb contact away from home 2.3 [1.2-4.6]
Robertson_EpiInf_2002* Australia Calf contact away from home 2.9 [1.5-5.7]
Robertson_EpiInf_2002 Australia Calf contact away from home 2.5 [1-6.4]
Robertson_EpiInf_2002 Australia Lamb contact away from home 0.5 [0.1-2.1]
Robertson_EpiInf_2002* Australia Calf contact away from home 5.1 [1.5-17.3]
Roy_JCM_2004* USA Contact with calves and cows 3.4 [2-5.8]
Roy_JCM_2004* USA Contact with calves and cows 3.5 [1.8-6.8]
Valderrama_EpiInf_2009 USA Contact with cows; sheep; goats 1 [0.4-2.8]
Yang_IDP_2017 China Keep livestock or poultry 2.04 [1.05-3.98]
Yang_IDP_2017* China Keep livestock or poultry 2.27 [1.01-5.08]
Yang_IDP_2017 China Living under same roof with livestock 0.65 [0.19-2.19]
Wilson_EPI_2008 NewZealand Farm animals 2.8 [2.4-3.4]
Random Effect Meta-Analysis All 2.17 [1.7-2.76]
0.10
1.0
2.0
5.0
10.0
15.0
25.0


Study | Country | Label | Odds Ratio | [95% CI]
Fournet_Eurosurveillance_2013 | Netherlands | Contact with surface water | 1.15 | [0.63-2.1]
Gallaher_AJPH_1989 | Mexico | Swim in surface water | 3.7 | [1.02-13.5]
Goh_EID_2004 | UK | Swimming pool | 0.94 | [0.61-1.44]
Hellard_STI_2003 | Australia | Swimming | 1.75 | [0.25-12.5]
Hunter_EID_2004* | UK | Swam in a toddler pool | 1.26 | [0.96-1.65]
Hunter_EID_2004 | UK | Swimming pool use | 1.15 | [0.86-1.55]
Hunter_EID_2004 | UK | Use of toddler pool | 1.52 | [1.01-2.28]
Khalakdina_BMCPH_2003 | USA | Swimming; hot tub/spring | 1.02 | [0.28-3.75]
Marder_Thesis_2012* | USA | Recreational water | 6.53 | [6-7.12]
Marder_Thesis_2012* | USA | Recreational water - Treated | 8.8 | [7.96-9.73]
Marder_Thesis_2012* | USA | Recreational water - untreated | 4.77 | [4.25-5.37]
Mooij_NIPHE_2015* | Netherlands | Swam in river or lake | 5.26 | [2.5-11.06]
Mooij_NIPHE_2015* | Netherlands | Swam in the sea | 3.19 | [1.41-7.23]
Mooij_NIPHE_2015* | Netherlands | Scuba dived in a pool | 1.81 | [0.7-4.67]
Mooij_NIPHE_2015* | Netherlands | Swam in an inflatable pool | 1.26 | [0.82-1.94]
Mooij_NIPHE_2015* | Netherlands | Swam in river or lake | 4.9 | [2-12]
Mooij_NIPHE_2015* | Netherlands | Used inflatable pool | 2.42 | [1.54-3.81]
Mooij_NIPHE_2015* | Netherlands | Swallowed inflatable pool water | 0.77 | [0.38-1.52]
Mooij_NIPHE_2015* | Netherlands | Swallowed pool water | 2.09 | [1.28-3.42]
Mooij_NIPHE_2015* | Netherlands | Swam in a pool | 1.6 | [1.1-2.33]
Mooij_NIPHE_2015* | Netherlands | Swallow water during sports | 1.47 | [0.79-2.71]
Mooij_NIPHE_2015* | Netherlands | Swim in river or lake | 1.5 | [0.79-2.87]
Mooij_NIPHE_2015* | Netherlands | Swim in inflatable pool | 1.75 | [1.25-2.46]
Mooij_NIPHE_2015* | Netherlands | Swallow inflatable pool water | 1.78 | [1.03-3.08]
Mooij_NIPHE_2015* | Netherlands | Swim in pool | 1.65 | [1.23-2.19]
Mooij_NIPHE_2015* | Netherlands | Swallow pool water | 1.23 | [0.87-1.74]
Pintar_EpiInf_2009 | Canada | Went hiking; camping or canoeing | 2.1 | [0.8-5.7]
Pintar_EpiInf_2009 | Canada | Went swimming | 3.8 | [1.8-8.2]
Pintar_EpiInf_2009 | Canada | Swim pool | 1.9 | [0.8-4.8]
Pintar_EpiInf_2009 | Canada | Swim in natural water (lake or river) | 3.1 | [1.4-6.7]
Pintar_EpiInf_2009* | Canada | Swim in natural water (lake or river) | 2.91 | [1.14-7.38]
Ravel_EpiInf_2013 | Canada | Swam in the lake | 1.71 | [0.56-5.22]
Ravel_EpiInf_2013 | Canada | Swam in the pool | 3.25 | [0.82-12.96]
Ravel_EpiInf_2013 | Canada | Canoed; kayaked | 2.05 | [0.57-7.33]
Robertson_EpiInf_2002 | Australia | Swimming in public pool | 2.5 | [1.8-3.4]
Robertson_EpiInf_2002 | Australia | Swimming in public toddlers' pool | 2.3 | [1.5-3.4]
Robertson_EpiInf_2002 | Australia | Swimming in public adults' pool | 2.5 | [1.8-3.4]
Robertson_EpiInf_2002* | Australia | Swimming in public pool | 2.7 | [1.9-3.8]
Robertson_EpiInf_2002 | Australia | Swimming in public pool | 1.3 | [0.9-2]
Robertson_EpiInf_2002 | Australia | Swimming in public toddlersÂ´ pool | 1.9 | [1-3.6]
Robertson_EpiInf_2002 | Australia | Swimming in public adultsÂ´ pool | 1.3 | [0.9-2.1]
Robertson_EpiInf_2002* | Australia | Swimming in public pool | 1.2 | [0.8-1.9]
Roy_JCM_2004* | USA | Freshwater swimming | 1.6 | [1-2.5]
Roy_JCM_2004* | USA | Marine swimming | 2.6 | [1.2-5.6]
Roy_JCM_2004* | USA | Pool swimming | 1.3 | [0.8-1.9]
Roy_JCM_2004* | USA | Community/municipal pool swimming | 0.6 | [0.2-2.1]
Roy_JCM_2004* | USA | Subdivision/neighborhood pool swimming | 0.9 | [0.1-10.1]
Roy_JCM_2004* | USA | Kiddie/wading pool swimming | 3.6 | [0.9-14.2]
Roy_JCM_2004* | USA | Private pools swimming | 3.7 | [1-13.4]
Roy_JCM_2004* | USA | Waterpark swimming | 1.4 | [0.6-3.5]
Roy_JCM_2004* | USA | Freshwater swimming | 1.9 | [1-3.5]
Roy_JCM_2004* | USA | Marine swimming | 2.5 | [0.7-8.2]
Roy_JCM_2004* | USA | Pool swimming | 1.3 | [0.8-2.3]
Roy_JCM_2004* | USA | Waterpark swimming | 1 | [0.3-3.3]
Valderrama_EpiInf_2009 | USA | Recreational water | 1.8 | [0.9-3.8]
Valderrama_EpiInf_2009 | USA | Lake; pond; river | 2.1 | [0.8-5.5]
Valderrama_EpiInf_2009 | USA | Water sports | 0.5 | [0.1-3.1]
Valderrama_EpiInf_2009 | USA | Hot tubes; spas; jacuzzis | 1.1 | [0.4-2.7]
Valderrama_EpiInf_2009 | USA | Water park | 2 | [0.8-5]
Valderrama_EpiInf_2009 | USA | Swimming pool | 1.3 | [0.6-2.7]
Valderrama_EpiInf_2009 | USA | Spray prad; fountain | 0.8 | [0.2-2.7]
Valderrama_EpiInf_2009 | USA | Hot springs | 6 | [0.6-57.7]
Valderrama_EpiInf_2009 | USA | Recreational water in mouth | 1.6 | [0.6-3.8]
Valderrama_EpiInf_2009* | USA | Recreational water | 4.6 | [1.4-14.6]
Wilson_EPI_2008 | NewZealand | Recreational water | 3.5 | [2.8-4.4]
Random Effect Meta-Analysis | All | | 1.97 | [1.46-2.64]
0.10
1.0
2.0
5.0
10.0
15.0
25.0


Study
Country
Label
Odds Ratio
[95% CI]
Goh_EID_2004
UK
Raw sausages
1.56
[0.51-4.61]
Goh_EID_2004
UK
Other raw meat
1.93
[0.71-5.14]
Mooij_NIPHE_2015*
Netherlands
Ate filet American
1.12
[0.8-1.57]
Pintar_EpiInf_2009
Canada
Purchased meat at a butcher's
0.8
[0.2-3.5]
Pintar_EpiInf_2009
Canada
Killed own meat
2.3
[0.5-10]
Ravel_EpiInf_2013
Canada
Meat from other than groceries
2.54
[0.81-7.94]
Ravel_EpiInf_2013
Canada
Meat from private kill
2.16
[0.37-12.51]
Ravel_EpiInf_2013
Canada
Butcher shop
4.99
[1.01-24.58]
Ravel_EpiInf_2013
Canada
BBQ
2.12
[0.79-5.71]
Random Effect Meta-Analysis
All
1.93
[1.24-3.02]
0.10
1.0
2.0
5.0
10.0
25.0


Study
Country
Label
Odds Ratio
[95% CI]
Goh_EID_2004 UK Pasteurised milk 1.3 [0.72-2.36]
Goh_EID_2004 UK Unpasteurised milk 1.28 [0.53-3.02]
Goh_EID_2004 UK Local cheese 1.94 [0.54-6.71]
Goh_EID_2004 UK Other cheese 1.43 [0.91-2.27]
Goh_EID_2004 UK Yogurt 1.03 [0.66-1.63]
Goh_EID_2004* UK Ate non-locally produced cheese 1.49 [0.91-2.43]
Ravel_EpiInf_2013 Canada Unpasteurized milk 2.34 [0.4-13.57]
Robertson_EpiInf_2002 Australia Unpasteurized milk products 2 [0.7-5.5]
Robertson_EpiInf_2002 Australia Unpasteurized milk products 3.9 [1.2-12.4]
Valderrama_EpiInf_2009 USA Unpasteurized milk 2 [0.1-32]
Random Effect Meta-Analysis All 1.53 [1.01-2.33]
0.10
1.0
2.0
5.0
10.0
25.0