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Risk factors for sporadic salmonellosis: a systematic review and meta-analysis

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Short Title

Meta-analysis on risk factors for sporadic salmonellosis

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Highlights ***(maximum 85 characters, including spaces, per bullet point).***

- Meta-analysis of 62 case-control studies about sporadic human salmonellosis
- Travel, environmental, animal and food exposures were significant risk factors
- Recent use of anti-acids or antibiotics and underlying disease increased the risk
- Known risk factors such as eggs and meat products were confirmed
- The role of consumption of raw or undercooked eggs and undercooked poultry is underlined
- Produce and milk formula are risk factors of salmonellosis for children

Keywords: Research synthesis; Case-control studies; Meta-regression; *Salmonella*

Abstract

Non-typhoidal *Salmonella* is an important causative agent of diarrheal illness worldwide. A systematic review and meta-analysis of case-control studies were performed to determine the main risk factors associated with sporadic salmonellosis. Suitable scientific articles published up to 2017 were identified through a systematic literature search and subject to methodological quality assessment. From each study, odds ratios (OR) were extracted or calculated, as well as study characteristics such as population type, design, type of model used and risk factor categorization. Mixed-effects meta-analytical models were adjusted by population type to appropriate data partitions. From 3858 identified references, the quality assessment stage was passed by 62 case-control studies focusing on sporadic salmonellosis which provided 1154 ORs for meta-analysis.

The meta-analysis identified host-specifics factors, travel, environmental, animal and food exposures as significant risk factors of salmonellosis in the mixed population. For the mixed population, foods significantly associated with salmonellosis were eggs and egg products, composite foods, and meat (pork, red meats other than beef and poultry meats). In the child

population, the main risk factors were found for person-to-person transmission, recent use of gastric anti-acids or antibiotics, contact with pets and farm animals, environmental, and food vehicles. Breastfeeding was found to be a protective factor for children. The food vehicles identified in children comprised dairy (milk formula), produce, meat and eggs products. Untreated drinking water was a risk factor for the children and mixed population. The result of the meta-analysis conducted at the international level is very important in the context of increasing international trade in foodstuffs and changes in food consumption patterns.

Introduction

Non-typhoid *Salmonella enterica* subsp. *enterica* is a major foodborne pathogen that causes mild to moderate self-limiting gastroenteritis (WHO, 2018). Salmonellosis is usually characterized by acute onset of fever, abdominal pain, diarrhea, nausea and sometimes vomiting. The onset of disease symptoms occurs 6–72 hours (usually 12–36 hours) after the ingestion of *Salmonella*, and the illness lasts 2–7 days (WHO, 2018). Patients will make a recovery without specific treatment in most cases.

Salmonellosis is the second most frequently reported bacteriologically related zoonosis in many European countries (EFSA and ECDC, 2018). In France, the annual community incidence rate was estimated at 307 cases per 100,000 for salmonellosis (Van Cauteren et al., 2015; Van Cauteren et al., 2017). Microbiological and epidemiological investigations make it possible to identify outbreaks and to trace back the food at the origin of the human cases (Inns et al., 2015; Ung et al., 2019). Although *Salmonella* outbreaks are identified, a majority of salmonellosis cases is not associated with any known outbreak (Glass et al., 2015) and are classified as sporadic cases. The question of specific food exposures and respective weight for these specific forms arise.

There are several methodological approaches for salmonellosis source attribution (Pires et al., 2010, Mughini-Gras et al., 2018), and the most appropriate approach depends on the data availability and research question to be addressed. A large variety of approaches has been explored, including microbial subtyping method (David et al., 2013 a,b; Barco et al., 2013 & 2015; Mikkelä et al., 2019), genomics approach (Zhang et al., 2019), comparative exposure assessment (Christidis et al., 2020), outbreak data analysis (Pires et al., 2010; Painter et al., 2013; IFASC, 2019), or expert elicitation (Havelaar et al., 2008).

Another way of identifying the sources of these sporadic cases is case-control studies (Domingues et al., 2012). In case-control studies, the association of cases with various food exposures is usually measured through odds ratios (ORs) (Pires et al., 2009). Meta-analyses of these studies can provide information on exposure pathways of interest (Devleesschauwer et al., 2019). Domingues et al (2012) conducted a meta-analysis comprising thirty-five

Salmonella case-control studies identified through a literature search conducted in February 2008.

The aim of the present study is to perform an updated systematic review of case-control studies for human salmonellosis published internationally up to May 2017 and perform a meta-analysis to synthesize data on factors associated with sporadic *Salmonella* infection, combining the odds ratio from a selection of relevant studies (Gonzales-Barron et al., 2019).

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). The screening criteria followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

Systematic review

The keywords were defined attending the review question which is to evaluate the association between a (risk) factor and sporadic salmonellosis risk in a population exposed to it. This review question was identified to have a typical PECO structure (Population, Exposure, Comparator and Outcome as key elements). The literature search was conducted in March 2017 using a combination of keywords related to (1) "*Salmonella* OR salmonellosis", (2) "case-control" OR "risk factor" OR "cohort (3) "infection" OR disease"", joined by the logical connector AND.

Systematic searches using a combination of suitable keywords were conducted using the bibliographic engines Science Direct, PubMed, Scielo, ISI Web of Science and Scopus. The literature search was limited to the English, French, Portuguese and Spanish languages.

Each reference record was screened for relevance for inclusion in the meta-analysis study, and subsequently, the methodological quality of the "candidate" studies was assessed using preset quality criteria. Five criteria for inclusion were related to the definition of disease. First, it had to refer to confirmed humans salmonellosis. The second criterion refers to the study design whereby only case-control studies were considered. The third criterion is the presence of information on cases definition. Finally, the quality and the completeness of statistical analysis were assessed. Primary studies that passed the screening for relevance were marked as having the potential for bias if they failed to meet at least one of the methodological quality assessment criteria. Studies related to *S*. Typhi and Paratyphi were excluded from the review.

Data from primary studies were then extracted using a standardised spreadsheet. Data extracted included the relevant study characteristics (location, period, population, serotype, 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 (Odds Ratio (OR)). A data categorisation scheme was established to hierarchically group the risk factors into travel, host-specific factors and pathways of exposure (see the methodological paper of this issue Gonzales-Barron et al., 2019). The variable "population" was stratified into mixed (adults, or undefined age), and children.

Data synthesis

As described in Gonzales-Barron et al. (2019). The joint meta-analytical data was first described using basic statistics. Next, data was partitioned into subsets of categories of risk factors. Meta-analysis models were then fitted to each of the data partitions or subsets in order to estimate the overall OR for travel, host-specific factors and transmission pathways related to person-to-person transmission, animal contact, environmental and food exposures. The meta-analytical models were fitted separately by population type. For some food classes, the effects of handling (i.e., eating raw, undercooked) and setting (i.e., eating out) on the overall ORs were assessed by calculating the ratio of the mean ORs when food was mishandled (or when food was prepared outside the home) to the base ORs.

The statistical analysis was designed to assess the effect of the geographical region, the study period and the analysis type (univariate/multivariate) on the result. The objective of the region-specific meta-analysis was to inform the decision on the geographical regions that should be kept for the subsequent pooling of ORs. All meta-analytical models were essentially weighted random-effects linear regression models. Once a meta- analytical model was fitted, influential diagnostics statistics based on Cook's distance were assessed to remove any influential observation originating from studies marked as having potential-for-bias. Publication bias was assessed by funnel plots and statistical tests investigating the effect of the study sample size on the ORs (Gonzales-Barron et al., 2019). Heterogeneity

146 between studies was assessed by three indicators, the between-study variability (τ^2), the QE
147 test investigating residual heterogeneity, the variance of residuals and the intra-class
148 correlation I^2 (Gonzales-Barron et al., 2019).
149 All analyses were conducted in the R software implemented with the *metafor* package
150 (Viechtbauer, 2010).
151 Pooled ORs were considered as significant when the lower bound of the 95% CI was equal
152 or greater than one, except for breastfeeding where the upper bound of the confidence
153 interval had to be below one for it to be deemed as significant (protective).

154

155 **Results**

156 **Descriptive statistics of the case-control studies**

157 From 3858 identified and analyzed references, 460 passed the relevance screening and 62
158 passed the quality assessment stage (Fig. 1). Appendix 1 summarizes the 62 bibliographic
159 references. Appendix 2 summarizes the main features (country, population, period, design,
160 model, number of cases/controls, quality and numbers of ORs) of the 62 case-control studies
161 used in this meta-analysis. These case-control studies constitute a set of 1,154 ORs from
162 risk factors (above 0.5 except for breastfeeding).
163 These published studies were conducted in years spanning from 1987 and 2013 (51.6 % are
164 after 2000). Most publications concerned Europa (29 publications), North America (25
165 publications), followed by Oceania (5 publications), Asia (2 publications) and South America
166 (1 publication). Europe provided 51% of the ORs (588/1154) while North America (United
167 States, Canada) is also highly represented with 40% of ORs (455/1154).
168 Most studies investigated exposures in the mixed population (adults or non-precise age, 48
169 publications), followed by child population (16 publications) and susceptible (HIV infected
170 patients) (1 publication) (Appendix 1) (Taconelli et al., 1998). This last publication only
171 contributes to the analysis with one OR concerning antibiotics in host-specific factors.

172 Except for one study (Bellido-Blasco et al., 2007), salmonellosis cases were confirmed by
173 isolation of the bacterium. A diversity of serotypes is considered in the 62 studies but the
174 majority (50%) retained only *S*. Enteritidis and *S*. Typhimurium.
175 The risk factors studied concerned the following routes of exposure: person-to-person (19
176 OR), environmental (84 OR), contact with animals (175 OR), and food or handling practices
177 (700 OR). Host-specific factor (122 OR) or travel (54 OR) are also studied in this work.
178 After methodological quality assessment, 13 case-control studies were marked as being
179 below standards (as example controls have campylobacteriosis) and corresponding ORs
180 were removed from the meta-analysis if sensitivity analysis found an influence on the pooled
181 estimate (Gonzales-Barron et al., 2019*)*.

182 **Meta-analysis**

183 For every data partition, the meta-analysed risk factors are presented in summary tables only
184 when significant (Tables 1, 2 and 3). Non-significant results or significant pooled ORs coming
185 from a single study for main risk factors are given in Table 4.

186 **Significant risk factors associated with travel, host-related factors, contact with the**
187 **environment and animals**

188 Table 1 presents the significant risk factors for these main factors explored. In all
189 geographical regions, except for case-control studies carried out in Asia, travel was a
190 significant risk factor for salmonellosis. Thus, for the estimation of the travel subcategories,
191 the data points from Asia were removed. Both inside and abroad travels were found to be
192 associated with an increased risk of sporadic salmonellosis (pooled OR of 3.612 95% CI
193 [2.839 - 4.593] and 2.195 95% CI [1.054 - 4.572] respectively. It is worth noticing that before
194 the year 2000, the travel associated OR was significantly higher (p=0.005).
195 Several host-specific factors were associated with the risk of salmonellosis. The use of
196 gastric anti-acids or antibiotics had ORs above 3.0 in the mixed population (Table 1) (anti-
197 acids: pooled OR 3.184 95% CI [2.449 - 4.139]). Patients with chronic diseases (i.e.
198 allergies, stomach ulcer, cancer, diabetes, endocrine disease, heart disease, kidney disease,

intestinal disorders, alcoholism, autoimmune disease, and blood disorder) had also significantly higher odds of acquiring salmonellosis (pooled OR=3.289 95% CI [2.449 - 4.416]). The same level of odds was observed in patients receiving other medications, such as NSAID, corticosteroids, thyroid and hormone drugs (pooled OR=4.655 95% CI [3.458 - 6.266]). When focusing on children, the use of anti-acids (pooled OR=3.413 95% CI [1.851 - 6.296]) and antibiotics (pooled OR=2.376 95% CI [1.618 - 3.489]) produced a similar degree of salmonellosis risk. In the population of infants, breastfeeding was proven to be protective against *Salmonella* infection. Combining the results from seven case-control studies, 747 infants of age lower than 2 years had a pooled OR of 0.249 95% CI [0.165 -0.377] times the odds of becoming ill than those who were not breastfed.

Person-to-person transmission was a significant risk factor for both the mixed population and children, but it was much higher in the latter, with a pooled OR of 1.692 95% CI [1.145 - 2.500] and 3.811 [1.977 - 7.348], respectively. Person-to-person transmission was described in the mixed population as contact with patient or contact household member with diarrhea (or confirmed cases). For the child population, contacts were described as contact with diarrhea in household or creche with an ill child.

Contact with animals (farm, pet or wild) for children as well as in the mixed population was an exposure pathway widely explored in the different studies (127 ORs for 30 studies in the mixed population, and 44 ORs from 9 studies for children). In the mixed population, the pooled ORs for this route of exposure ranged from 1.471 to 2.619 (contact with pets, on-farm activities, or professional activities related to animals and carcasses, and contact with wild animals). Farm environment was also found to be a risk factor in the mixed population (pooled OR 1.900 95% CI [1.251 - 2.885]). For children, the pooled ORs associated with contact with pets and farm animals were 3.035 95% CI [1.938 - 4.756] and 2.658 95% CI [1.431 - 4.938], respectively. When exploring in more detail the pet factor, for both populations, the diversity of animals was important (reptiles, dogs, cats, pets with diarrhea, etc.). The categories of farm animals and wild animals were also very diverse.

For the mixed population, salmonellosis cases occurred more frequently among people exposed to water-related activities (fishing, swimming, sailing, etc.) (pooled OR=2.221 95% CI [1.339 - 3.681]). Drinking water practice was also significantly associated with increased salmonellosis risk. Within this category, the consumption of untreated water was associated with salmonellosis for the mixed population (pooled OR=1.753 95% CI [1.109 - 2.770]) and represented a risk factor specifically for children too (pooled OR=2.130 95% CI [1.285 - 3.532]) (Figure 2). For children, outdoor activities (activities in parks, playground sandboxes, contact with soil, etc.) were strongly associated with salmonellosis (pooled OR=3.055 95% CI [2.243 - 4.160]). Childcare attendance was significantly associated with salmonellosis (pooled OR=2.738 95% CI [2.243 - 4.160]) in children, but strength or ORs were very different in different childcare settings (e.g. school, daycare).

Significant risk factors associated with food-related transmission pathways

Significant factors associated with food are given in Tables 1, 2 and 3. The studies explored a wide range of foods and food preparation/consumption practices (e.g. hygiene, cooking, and place of consumption). For the mixed population foods significantly associated with salmonellosis were eggs and egg products (pooled OR=1.774 95% CI [1.351 - 2.329]), composite foods (pooled OR=1.731 95% CI [1.258 -2.381]), and meat (pooled OR=1.489 95% CI [1.137 - 1.951]) (Table 1). Within eggs category, higher pooled OR values were obtained for egg products (pooled OR=2.736 95% CI [1.502 - 4.987]) compared to eggs (pooled OR= 1.976 95% CI [1.138 - 3.431].

Among meats, poultry (pooled OR=1.474 95% CI [1.167 - 1.861]), pork (pooled OR=1.563 95% CI [1.111 - 2.200), red meats other than beef (pooled OR=1.680 95% CI [1.044 - 2.703])(as lamb, mutton or venison meat), and other meats (pooled OR = 1.938 95%CI [1.215 - 3.091]) were the most important risk factors in the mixed population (Table 2).The category “others” is very heterogeneous containing meats of non-specified origin. The food vehicles identified in children also comprised meat and eggs categories (Table 1). For meat products, pork had the highest pooled OR (pooled OR=3.089 95% CI [1.348 - 7.078])

253 followed by processed meat products (pooled OR=2.122 95% CI [1.538 - 2.928]) and beef
254 (pooled OR=1.623 [1.072 - 2.473]). Produce and dairy were also significantly associated with
255 increased risk of salmonellosis in children (Table 1). The association with dairy, here
256 described as milk formula, was explained by a pooled OR of 3.324 95% CI [2.136 - 5.172]
257 (Figure 3 and Table 2).
258 The consumption of undercooked pork and poultry meat multiplied the basic ORs by a factor
259 of 3.038 and 3.986, respectively (Table 3). Consumption of raw or undercooked eggs
260 increased the basic ORs by a factor of 3.642 and 2.182, respectively. Out-of-home
261 consumption of poultry, eggs or processed meats increased the basic ORs by factors
262 ranging from 1.5 to 2 (Table 3).
263 For most of the meta-analytical models (models) reported in legends of Tables 1, 2 and 3,
264 the statistical tests indicated the absence of potential significant publication bias is above
265 5%. An exception is observed in the partitions related to host-specific and food in the mixed
266 population (Table 1), dairy in children (Table 2), and the effect of handling on the
267 consumption of poultry and processed meat (Table 3). For better assessing the publication
268 bias (above 5%), the funnel plot for those models is given in Figure 4. All of them exhibited
269 asymmetry, as lack of non-significant studies with smaller ORs which could lead to OR
270 overestimation. Moreover, the intraclass correlation I^2 were for all partitions below high
271 heterogeneity (<75%). However, residual between-study heterogeneity (p-value often below
272 0.05 for Q or QE) was observed for the data partitions.

Discussion

In this study, the aim was to perform an updated systematic review of case-control studies for human salmonellosis and to synthesize data in order to reveal the weight of common factors associated with sporadic *Salmonella* infection, among them the relative importance of travel, host-related factors, contact with animals and the environment, as well as food-related factors. Based on the results of the meta-analysis, the ORs associated with non-food risk factors (ORs between 2 and 6) were higher than those associated with exposures to main foods categories (ORs between 1.4 and 2.9). In agreement with the scientific literature (Domingues et al., 2012; Johnson et al., 2011), the present study identified international travel as a significant risk factor for salmonellosis. Although the number of studies was relatively small, the meta-analysis also allowed for the identification of within-country travel as a significant risk factor; the considered case-control studies concerned large countries, i.e. Australia (Ashbolt and Kirk, 2006) and the US (Passaro et al, 1996, Trepka et al, 1999). Another hypothesis to explain this risk factor is associated with the consumption habits during travelling. Indeed, this risk factor might be a reflection of more frequent eating out practices, which have been also found to be a significant risk factor.

The present meta-analysis also confirmed the findings of Domingues et al. (2012) in the relation to the importance of medication and chronic diseases. Concerning the latter factor, it is worth mentioning that Teunis et al. (2010) did not observe significant differences between the salmonellosis dose-response relations obtained for general and susceptible populations.

The evidenced strong effects of non-food exposures in this meta-analysis suggest that the risk of acquiring salmonellosis is multi-factorial and that other sources than the foodborne ones, such as contact with animals (Hoelzer et al., 2011; Lambertini et al., 2016) and environmental waters (Guillier et al. 2020), are worth investigating too.

The food risk factors identified in the meta-analysis were corroborated by the analysis of epidemiological data. Consumption of raw eggs, undercooked pork, poultry, beef, and milk formula regularly cause outbreaks (Guillier et al., 2013; Dallman et al., 2016; Jones et al., 2016; Dewey-Mattia et al., 2018). The data collected by the European RASFF (Rapid Alert

301 System for Food and Feed) system also confirm the importance of these categories. Of the
302 170 notifications from the EU Member States, poultry meat ranks first in terms of number of
303 alerts, followed by other meat and eggs and egg products (RASFF 2017). Similar to
304 Domingues et al. (2012), the consumption of dairy products was not found to be significant in
305 the mixed population despite the frequent link between raw milk cheese consumption
306 and *Salmonella* outbreaks (Yoon et al., 2016).
307 A potential difficulty to interpret the results of the meta-analysis could be due to the strong
308 host specificity of some serovars (Vila-Nova et al., 2019). Indeed, the salmonellosis cases in
309 the considered case-control studies are either caused by specific and frequently occurring
310 serovars (i.e. Typhimurium and Enteritidis, in particular) or by many different serovars. While
311 some serovars are not strongly associated with a unique animal reservoir (e. g. Typhimurium
312 or Agona), others display strong associations with reservoirs, such as Enteritidis and layers,
313 Derby and pigs, Dublin and cattle (Langridge et al., 2014). This may partly explain the
314 variability in ORs in the different case-control studies, and the remaining heterogeneity
315 between studies. For example, the ORs associated with egg consumption in studies focusing
316 only on Enteritidis were likely to be higher than those from studies of other serovars. The
317 importance of serovar in risk factor analysis has been shown recently (MacDonald et al.,
318 2018); their results supported the notion that the epidemiology of *S*. Typhimurium may differ
319 from other *Salmonella* types leading to differences in risk factors.
320 Besides, the relative importance of serovars in sporadic cases may differ between continents
321 and reflect very different epidemiological situations (Ferrari et al., 2019). For example, the
322 Heidelberg and Newport serovars are important and original in their representation in
323 salmonellosis cases for the North American continent (Jackson et al., 2013), while they are
324 not very important in the EU. Moreover, the different food consumption behaviors and habits
325 in the countries where the case-control studies were carried out may have had an impact, as
326 e.g. some kinds of meat may be mostly consumed undercooked by some, but not by others.
327 For example, in France, the consumption of undercooked beef is a common
328 practice (ANSES, 2017) and this consumption practice has been described as a major risk

factor for Typhimurium and Enteritidis serovars (Delarocque-Astagneau et al., 2000; Delarocque-Astagneau et al., 1998). Snary et al. (2016) have shown that there is large variability concerning the type and frequency of consumption of pork products within the EU. These consumption patterns greatly impact the level of risk of pork products. On the other hand, the results of the meta-analysis conducted at the international level is very important in the context of increasing international trade in foodstuffs (Ercsey-Ravasz et al., 2012; Garre et al., 2019) and changes in food consumption patterns (Smith and Fazil, 2019). Indeed, this internationalization of trade and changes in consumer attitudes may lead to a change in risk. In this context, the identification of risk factors at the international level is, therefore, an important element for epidemiologists who often have a historical view of the different routes of transmission and specific to their country.

At this stage, the ORs cannot be used to estimate the population attributable fraction in a risk assessment. Indeed, the overall values of ORs might have been modulated by the different regulatory measures at the international level (e.g. for the table egg sector in Europe versus other continents) or within Europe (e.g. Sweden applies more stringent management measures for cattle herds than those adopted by European regulations (Ågren et al., 2015)).

The published case-control studies included this meta-analysis are stored in a database, which will be updated with other relevant studies published in the future. This opens the way for further analyses, providing a basis for comparison between different countries about the risk for salmonellosis associated with exposure to a given risk factor. Analysis of ORs observed in different countries in relation to their regulations might also indicate the appropriateness of management measures to be adopted. This basis should also make it possible to carry out various studies focusing on specific serovars, in particular Enteritidis and Typhimurium, in the future. Examination at this level would be a key element for tracing the sources of sporadic cases.

Conclusion

The results of this meta-analysis confirm the outcomes obtained in a previous systematic review of case-controls studies of salmonellosis (Domingues et al., 2012). Moreover, they help going beyond the usual suspect of egg products being always the source and stress the importance of refining the assessment of other food vehicles and consumption practices, and routes such as environmental and animal contact.

The contribution of environmental or animal contact to the risk of sporadic salmonellosis should be better documented in dedicated studies. It may be appropriate to include factors related to professional activities, and those relating to contact with pets. Finally, risk factors should be investigated by *Salmonella* serovars. Such investigations could enable for the identification of source-specific risk factors and underlying transmission pathways.

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569 **Appendix**

570 **Appendix-1. Bibliographic references of the case-control studies for *Salmonella* spp**

571 **Appendix- 2. Characteristics of the 62 case-control studies investigating sources of**

572 **sporadic human salmonellosis included in the meta-analysis**

Figure captions

Figure 1. PRISMA flow chart of the literature search for case-control studies of human salmonellosis

Figure 2. Forest plot of the associations of salmonellosis with consumption of untreated /not enough treated drinking water in the mixed population (horizontal axis is expressed as OR in logarithm scale).

Figure 3. Forest plot of the associations of salmonellosis with consumption of dairy products in children (OR in logarithm scale)

Figure 4: Funnel plots of studies investigating categorized risk factors (host specific in mixed population, food in mixed population, dairy in children, handling poultry and handling processed meat)

Tables

Table 1. Results of the meta-analysis for the main risk factors

Population	Geographical area	Risk factor	Pooled OR [IC95%]	N/n*	p-value of risk factor	Publication bias p-value	Points removed **	Heterogeneity analysis***
Travel								
Mixed(y)	Asia excluded	Abroad	3.612 [2.839 - 4.593]	**18/47**	<.0001	0.408	1	τ2=0.0624 QE(df = 49) = 123.6, p-val < .0001 s^2=0.925 ; I^2=6.319%
		Inside	2.195 [1.054 - 4.572]	**3/3**	0.036			
Host specific								
Mixed(y)	All	Antiacids	3.184 [2.449 - 4.139]	12/31	<.0001	<.0001	0	τ2=0.6956 QE(df = 88) = 866.970, p-val < .0001 s^2=0.533; I^2=56.626%
		Antibiotics	3.348 [2.657 - 4.219]	14/30	<.0001			
		Chronic diseases	3.289 [2.449 - 4.416]	8/21	<.0001			
		Other medical conditions	4.655 [3.458 - 6.266]	5/11	<.0001			
Children	All	Antiacids	3.413 [1.851- 6.296]	2/3	<.0001	0.501	0	τ2=0.278 QE(df = 24) = 31.053, p-val = 0.152 s^2=0.500; I^2=35.724%
		Antibiotics	2.376 [1.618 - 3.489]	6/12	<.0001			
		Breastfeeding	0.249 [0.165 - 0.377]	7/12	<.0001			
Person to person								
Mixed	All		1.692 [1.145- 2.500]	7/10	0.008	0.056	0	τ2=0.557 QE(df = 17) = 58.734, p-val < .0001 ; s^2=0.82; I^2=40.425%
Children			3.811 [1.977- 7.348]	7/9	<.0001			
Animals								
Mixed	All	Pets	1.471 [1.189 - 1.821]	26/71	<.0001	0.283	1	τ2=1.1449 QE(df = 123) = 464.3872, p-val < .0001 ; s^2=0.605; I^2=65.420
		Exotic (new) pets	2.619 [1.763 - 3.894]	7/25	<.0001			
		Farm animals	1.937 [1.394 - 2.693]	9/19	0.0004			
		Occupational exposure	1.737[1.175 - 2.567]	5/12	0.0056			
Children	**All**	Pets	3.035 [1.938 - 4.756]	9/36	<.0001	0.731	1	τ2=0.369 QE(df = 41) = 76.2961, p-val = 0.0007; s^2=0.540; I2=40.63%
		Farm animals	2.658 [1.431 - 4.938]	2/5	0.002			
Environment								
Mixed	**All**	Recreational water	2.221 [1.339 - 3.681]	9/12	0.0020	0.088	0	τ2=0.7714 QE(df = 45) = 132.6221, p-val < .0001; s^2=0.594; I^2=56.48%
		Untreated drinking water	1.753 [1.109 - 2.770]	11/19	0.0162			
		Farm environment	1.900 [1.251- 2.885]	8/17	0.0026			
Children (at)	**All**	Untreated drinking water	2.130 [1.285 - 3.532]	5/8	0.0034	0.199	0	τ2= 0 QE(df = 27) = 31.5105, p-val = 0.2507 ;s^2=0.431 I^2= 0
		Daycare attendance	2.738 [1.658 - 4.522]	5/10	<.0001			

		Playground	3.055 [2.243 - 4.160]	6/13	<.0001			
Food								
Mixed	**All**	Meat	1.489 [1.137 - 1.951]	37/231	0.0039	0.035	8	τ2=0.215 QE(df = 537) = 1971.5989, p-val < .0001 ; s^2=0.792; I^2=21.34%
		Eggs	1.774 [1.351 - 2.329]	35/139	<.0001			
		Composite	1.731 [1.258 - 2.381]	16/66	0.0008			
Children	**All**	Meat	1.794[1.548 - 2.079]	8/34	<.0001	0.072	2	τ2= 0.6705 QE(df = 76) = 93.1415, p-val = 0.0884 s^2=0.482 ; I^2=58.178
		eggs	1.669[1.295 - 2.150]	7/20	<.0001			
		Dairy	2.828[2.067 - 3.870]	6/10	<.0001			
		Produce	2.099[1.169 - 3.768]	2/13	0.0130			

*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). **(y)**: year is significant (before/after 2000) in this model and the estimates are taking this effect into account; (at) analysis type is significant

597 **Table 2: Results of the meta-analysis on disaggregated risk factors (food)**

Risk Factor	Population	Geographical area	Risk factor precise	Pooled OR [IC95%]	N/n*	p-value of risk factor	Publication bias p-value	Points removed **	Heterogeneity analysis***
Meat	Mixed	Asia and south America removed	Poultry	1.474[1.167 - 1.861]	29/93	0.0011	0.202	2	τ2=1.93 QE(df = 218) = 917.4944, p-val < .0001 s^2=0.812 ; I^2=70.408%
			Other red Meats	1.680 [1.044 - 2.703]	5/10	0.0325			
			Pork	1.563 [1.111-2.200]	8/19	0.0103			
			Others	1.938 [1.215 - 3.091]	7/20	0.0054			
Meat (y)	Children	All	Beef	1.623 [1.072 - 2.473]	5/12	0.022	0.117	0	τ2=0.567 QE(df = 28) = 38.496, p-val = 0.089 s^2=0.54941 I^2=50.788
			Processed Meat	2.122 [1.538 - 2.928]	2/5	<.0001			
			Pork	3.089 [1.348 - 7.078]	2/4	0.007			
Eggs (at,y)	Mixed	Asia and south America removed	Eggs	1.976[1.138 - 3.431]	32/115	0.0155	0.592	0	τ2= 0.219 QE(df = 127) = 386.5163, p-val < .0001 ; s^2=0.769 I^2=22.197%
			Egg products	2.736[1.502 - 4.987]	7/16	0.0010			
Eggs (at)	Children	All	Multivariate analysis	1.557 [1.233 - 1.967]	3/5	0.0002	0.915	0	τ2=0 QE(df = 18) = 10.733, p-val = 0.905 s^2=0.228 I^2=0
			Univariate Analysis	1.464[1.272 - 1.685]	6/15	<.0001			
Dairy	Children	All	Milk formula	3.324 [2.136 - 5.172]	5/8	<.0001	0.014	0	τ2=0.111 Q(df = 7) = 9.665, p-val = 0.208 s^2=0.22810 I^2 : 0.228
Produce	Children	All		1.545 [1.314 - 1.819]	2/10	<.0001	0.535	0	τ2=0 Q(df = 9) = 8.4746, p-val = 0.4871 s^2=0.805 ; I^2=0
Composite	Children+mixed (all)	Asia removed	Dishes	1.609 [1.206 - 2.147]	16/46	0.0012	0.121	0	τ2=0.742 QE(df = 64) = 201.7201, p-val < .0001 s^2=0.569 I^2=56.574%
			Fast Food	1.443[1.053 - 1.977]	7/16	0.0226			
BBQ	All	All		1.952 [1.003 - 3.798]	4/7	0.0491	0.221	0	τ2=0.274 Q(df = 6) = 15.967, p-val = 0.0139 s^2=0.669 ; I^2=29.059%

*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). (y): year is significant (before/after 2000) in this model and the estimates are taking this effect into account; (at) analysis type is significant.

602 **Table 3. Effect of food handling on the pooled OR**

Risk Factor	Risk factor precise	Pooled OR [IC95%]	N/n*	p-value of risk factor	OR ratios and CI95%	Points removed **	Publication bias p-value	Heterogeneity analysis***
Poultry (at)	Eating Out	3.038 [1.965 - 4.697]	**12/24**	<.0001	1.961 [1.583- 2.429]	**3**	0.032	τ2=0.124 QE(df = 102) = 243.7902, p-val < .0001 s^2=0.593; I^2=17.311%
	Undercooked	3.986[1.641 - 9.681]	**6/8**	0.0054	2.572[1.322 - 5.005]			
	Poultry (base)	1.549[1.241 - 1.934]	**32/82 (ref eating out) 34/98 (ref handling)**	0.0001	**-**			
Processed Meat	Eating out	1.919 [0.922 - 3.994]	**7/13**	0.021	1.635 [1.074 - 2.487]	**2**	0.009	τ2=0.303 QE(df = 58) = 207.632, p-val < .0001 s^2=0.715 I^2=29.755%
	Processed Meat (base)	1.174 [0.858 - 1.606]	**17/48**	0.315	**-**			
Eggs (at)	Eating Out	2.575 [1.465 - 4.527]	**10/29**	0.0011	1.575 [1.199 - 2.069]	**3**	0.787	τ2=0.174 QE(df = 135) = 423.730, p-val < .0001 s2=0.818 I2=17.574%
	Undercooked	2.182 [1.388 - 3.428]	**22/49**	0.0004	1.335 [1.136 - 1.567]			
	Raw	3.642[1.776 - 7.469]	10/12	0.0002	2.228 [1.454 - 3.414]			
	Base eggs	1.635 [1.221- 2.188]	39/111(s) 31/79(h)	0.0009	–			
Pork meat	Undercooked	3.039[1.289- 7.163]	5/12	<.0001	3.578 [2.132- 6.002]	0	p= 0.259	τ2=0.1051 QE(df = 20) = 36.145, p-val = 0.0148 s^2=0.440 I^2=19.274%
	Base	0.849 [0.605 - 1.193]	7/11	0.3475	**-**			
Vegetables	Unwashed	1.542 [0.773- 3.073]	2/4	0.112	1.551[1.002 - 2.399]	0	p= 0.378	τ2=0.136 QE(df = 36) = 113.719, p-val < .0001 s^2=0.477 I^2=22.273%
	Base	0.994 [0.772- 1.281]	10/27	0.964	–			

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

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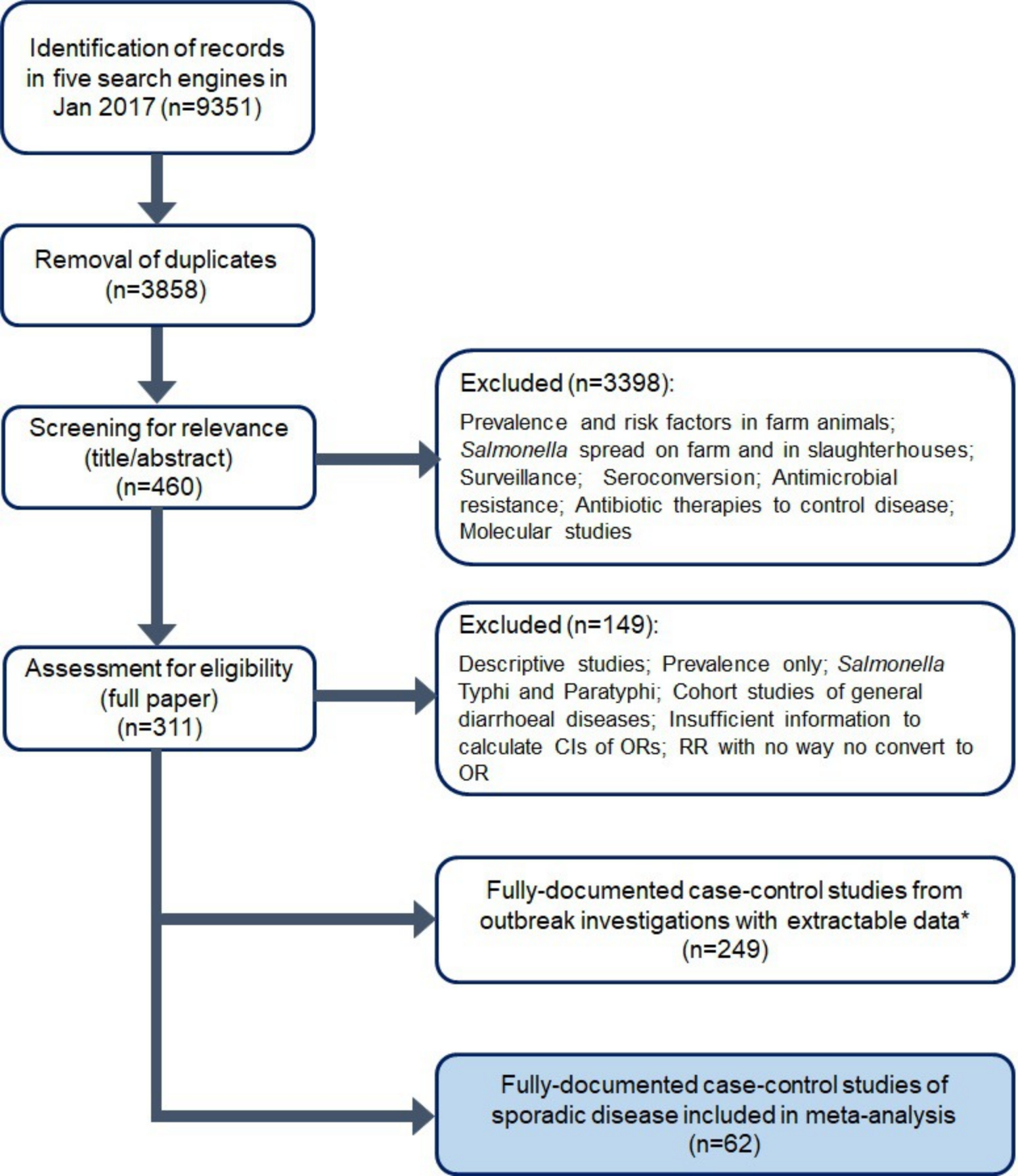
611 Table 4.Non significant or isolated *ORs* (1 publication) in main risk factors.

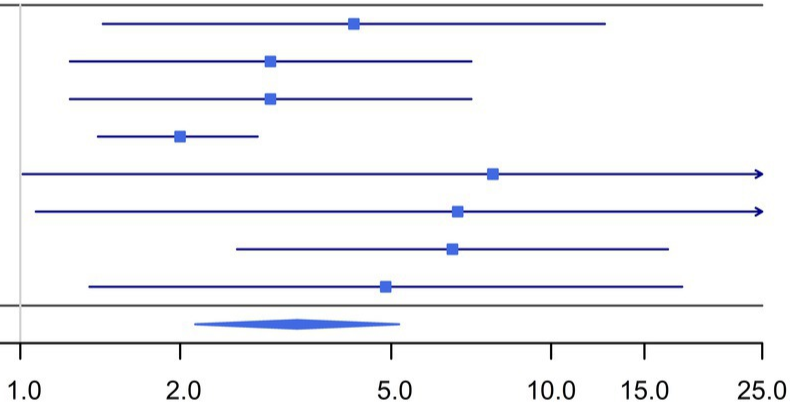
Population	Geographical area	Risk factor	Pooled OR [IC95%]	N/n*
Travel				
Mixed(y)	Asia excluded	Any	0.909[0.528- 1.565]	**2/3**
Animals				
Children	**All**	Exotic (new) pets	1.433[1.046- 1.962]]	1/3
Food				
Mixed	**All**	Produce	1.228[0.892- 1.690]	12/63
		Seafood	1.224 [0.795- 1.884]	6/10
		Dairy	1.187[0.850- 1.658]	13/31
		Beverages	1.535[0.887- 2.655]	3/4
Children	**All**	Seafood	1.387[0.637- 3.019]	2/4

612 N/n Number of studies/number of OR; if N=1 isolated studies: the result is not considered of significant

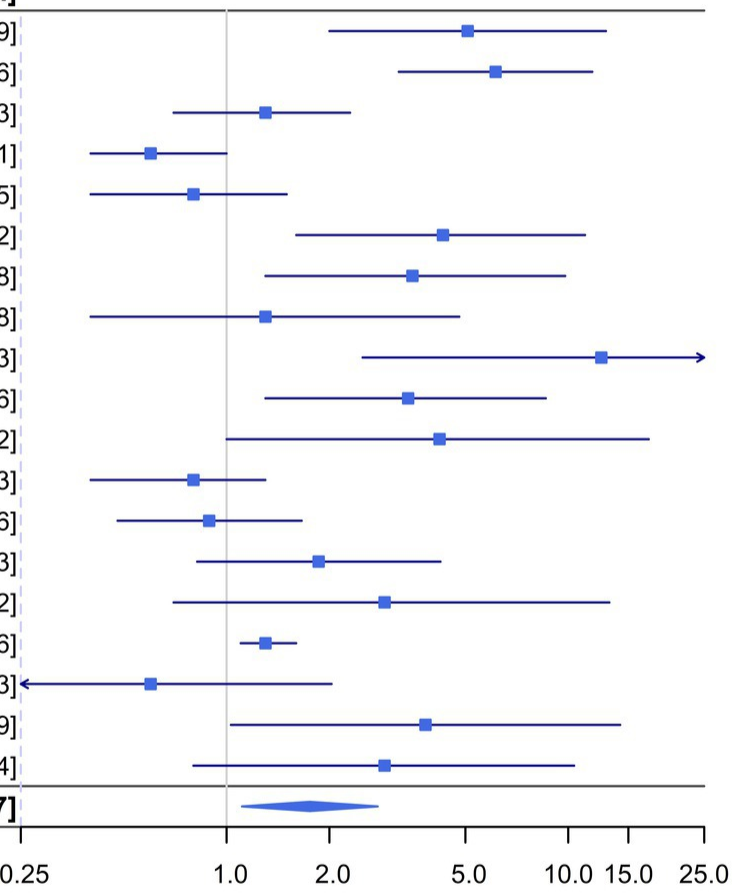
613 due to the lack of studies

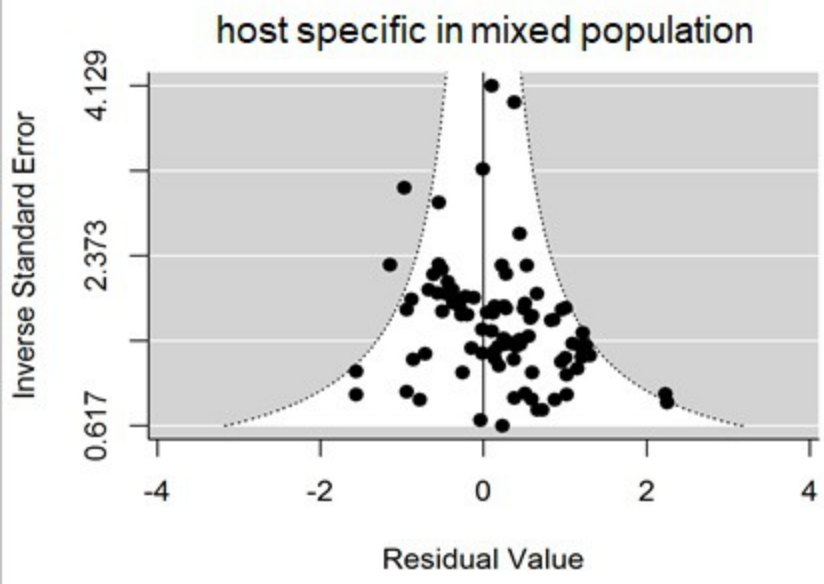

Identification of records in five search engines in Jan 2017 (n=9351)
Removal of duplicates (n=3858)
Screening for relevance (title/abstract) (n=460)
Excluded (n=3398):
Prevalence and risk factors in farm animals; *Salmonella* spread on farm and in slaughterhouses; Surveillance; Seroconversion; Antimicrobial resistance; Antibiotic therapies to control disease; Molecular studies
Assessment for eligibility (full paper) (n=311)
Excluded (n=149):
Descriptive studies; Prevalence only; *Salmonella* Typhi and Paratyphi; Cohort studies of general diarrhoeal diseases; Insufficient information to calculate CIs of ORs; RR with no way no convert to OR
Fully-documented case-control studies from outbreak investigations with extractable data* (n=249)
Fully-documented case-control studies of sporadic disease included in meta-analysis (n=62)

Study	Country	Label	Odds Ratio	[95% CI]
Bassal_EpiInf_2014	Israel	Milk formula	4.25	[1.43-12.63]
Haddock_AmJPubHealth_1991	Guam	Milk formula high iron	2.96	[1.24-7.08]
Haddock_AmJPubHealth_1991*	Guam	Milk formula high iron	2.96	[1.24-7.08]
Jones_Pediatrics_2006*	USA	Milk formula	2	[1.4-2.8]
Rowe_CID_2004	USA	Formula	7.77	[1.01-354.8]
Rowe_CID_2004*	USA	Liquid diet (formula/water)	6.67	[1.07-Inf]
Williams_JInfection_2016*	Australia	Formula	6.52	[2.56-16.61]
Williams_JInfection_2016*	Australia	Formula	4.88	[1.35-17.67]
Random Effect Meta-Analysis	**All**		**3.32**	**[2.14-5.17]**



Study	Country	Label	Odds Ratio	[95% CI]
Ashbolt_EpiInf_2006*	Australia	Untreated water	5.08	[2-12.9]
Ashbolt_EpiInf_2006*	Australia	Untreated water	6.13	[3.19-11.76]
Beard_NSW_2014	Australia	Untreated water	1.3	[0.7-2.3]
Dore_EpiInf_2004	Canada	Municipal drinking water	0.6	[0.4-1]
Dore_EpiInf_2004	Canada	Municipal drinking water	0.8	[0.4-1.5]
Clarkson_EpiInf_2009*	USA	Well water	4.3	[1.6-11.2]
Kapperud_AmJEpi_1998	Norway	Untreated water	3.5	[1.3-9.8]
Kapperud_AmJEpi_1998	Norway	Drinking surface source water	1.3	[0.4-4.8]
Kapperud_AmJEpi_1998	Norway	Untreated water supply	12.5	[2.5-63]
Kapperud_AmJEpi_1998	Norway	Private water supply	3.4	[1.3-8.6]
Kapperud_AmJEpi_1998*	Norway	Untreated water	4.2	[1-17.2]
Kapperud_EpiInf_1998	Norway	Untreated water	0.8	[0.4-1.3]
Kass_AEP_1992*	USA	Tap water	0.89	[0.48-1.66]
Kass_AEP_1992*	USA	Well water	1.86	[0.82-4.23]
Trepka_JID_1999	USA	Private well for drinking water	2.9	[0.7-13.2]
Wilson_EpiP&I_2008	New Zealand	Untreated water	1.3	[1.1-1.6]
Oggioni_AnnIg_2010*	Italy	Water from well or fountain	0.6	[0.18-2.03]
Oggioni_AnnIg_2010*	Italy	Surface water exc. well/fountain	3.82	[1.03-14.19]
Skjerve_ProcVetEpi_1991	Norway	Undisinfected water	2.9	[0.8-10.4]
Random Effect Meta-Analysis	**All**		**1.75**	**[1.11-2.77]**

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Inverse Standard Error
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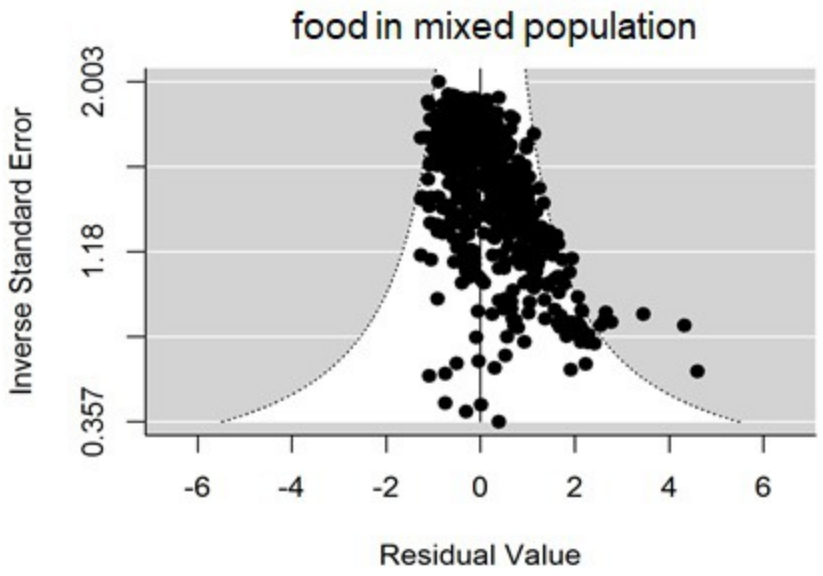
2.373
0.617
-4
-2
0
2
4
Residual Value


food in mixed population
Inverse Standard Error
2.003
1.18
0.357
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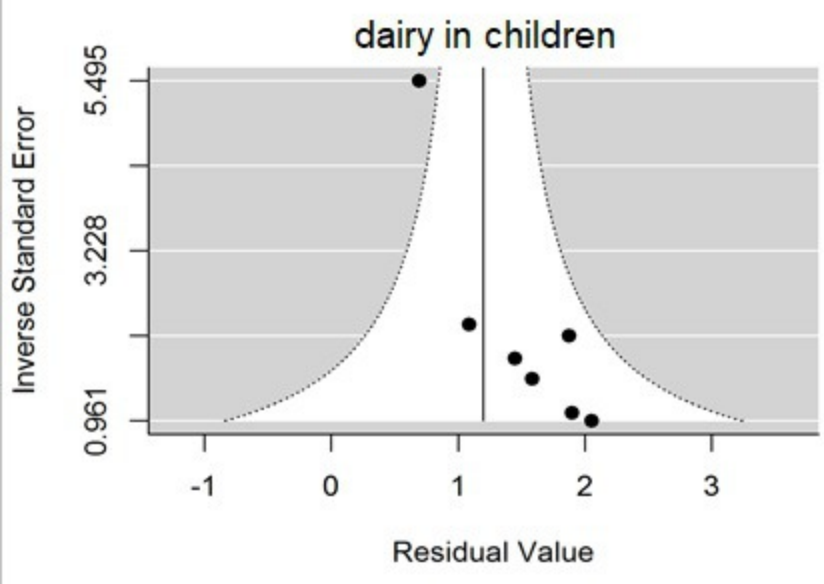
-4
-2
0
2
4
6
Residual Value


dairy in children
Inverse Standard Error
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3.228
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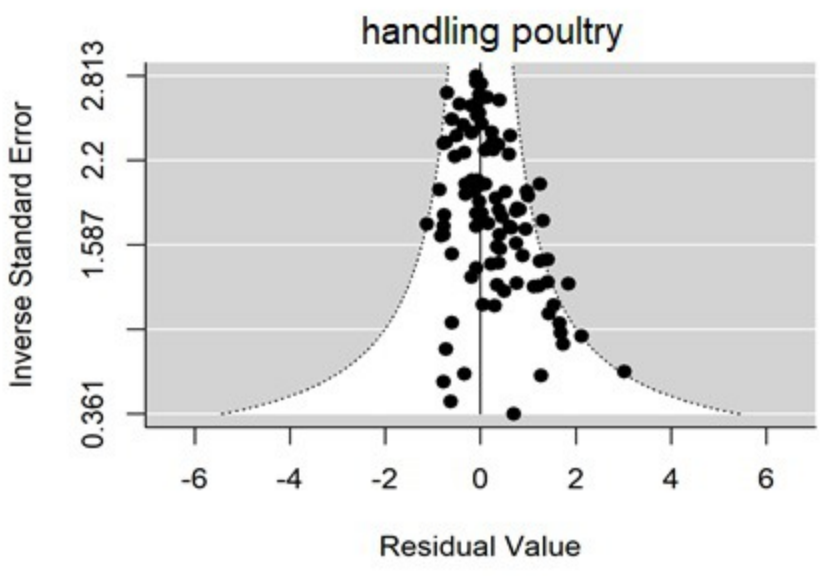
0
1
2
3
Residual Value


handling poultry
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1.587
0.361
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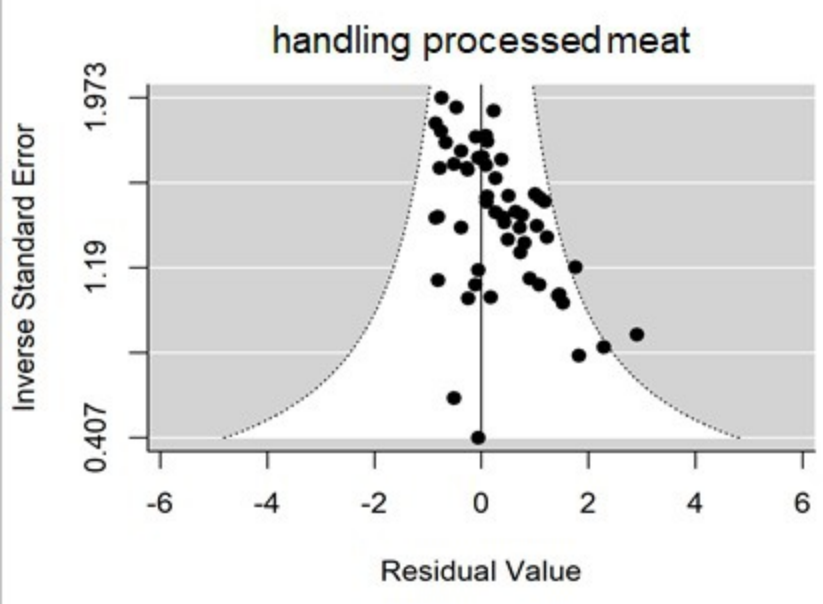
-2
0
2
4
6
Residual Value


handling processed meat
Inverse Standard Error
1.973
1.19
0.407
-6
-4
-2
0
2
4
6
Residual Value