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

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24 **Short Title**

25 Meta-analysis on risk factors for sporadic salmonellosis

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

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

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

35

36 **Abstract**

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

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

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

## 58 **Introduction**

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

65 Salmonellosis is the second most frequently reported bacteriologically related zoonosis in  
66 many European countries (EFSA and ECDC, 2018). In France, the annual community  
67 incidence rate was estimated at 307 cases per 100,000 for salmonellosis (Van Cauteren et  
68 al., 2015; Van Cauteren et al., 2017). Microbiological and epidemiological investigations  
69 make it possible to identify outbreaks and to trace back the food at the origin of the human  
70 cases (Inns et al., 2015; Ung et al., 2019). Although *Salmonella* outbreaks are identified, a  
71 majority of salmonellosis cases is not associated with any known outbreak (Glass et al.,  
72 2015) and are classified as sporadic cases. The question of specific food exposures and  
73 respective weight for these specific forms arise.

74 There are several methodological approaches for salmonellosis source attribution (Pires et  
75 al., 2010, Mughini-Gras et al., 2018), and the most appropriate approach depends on the  
76 data availability and research question to be addressed. A large variety of approaches has  
77 been explored, including microbial subtyping method (David et al., 2013 a,b; Barco et al.,  
78 2013 & 2015; Mikkela et al., 2019), genomics approach (Zhang et al., 2019), comparative  
79 exposure assessment (Christidis et al., 2020), outbreak data analysis (Pires et al., 2010;  
80 Painter et al., 2013; IFASC, 2019), or expert elicitation (Havelaar et al., 2008).

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

86 *Salmonella* case-control studies identified through a literature search conducted in February  
87 2008.

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

92

93 **Methods**

94 The protocol of the systematic review and the meta-analysis model are described in depth in  
95 the methodological paper of this special issue (Gonzales-Barron et al., 2019). The screening  
96 criteria followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses  
97 (PRISMA).

98 **Systematic review**

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

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

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

119 Data from primary studies were then extracted using a standardised spreadsheet. Data  
120 extracted included the relevant study characteristics (location, period, population, serotype,  
121 case definition, design, sample size of the groups, type of model, etc.), the categorized risk  
122 factors, the setting, the handling practices and the outcome of the study (Odds Ratio (OR)).  
123 A data categorisation scheme was established to hierarchically group the risk factors into  
124 travel, host-specific factors and pathways of exposure (see the methodological paper of this  
125 issue Gonzales-Barron et al., 2019). The variable “population” was stratified into mixed  
126 (adults, or undefined age), and children.

### 127 **Data synthesis**

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

137 The statistical analysis was designed to assess the effect of the geographical region, the  
138 study period and the analysis type (univariate/multivariate) on the result. The objective of the  
139 region-specific meta-analysis was to inform the decision on the geographical regions that  
140 should be kept for the subsequent pooling of ORs. All meta-analytical models were  
141 essentially weighted random-effects linear regression models. Once a meta-analytical model  
142 was fitted, influential diagnostics statistics based on Cook’s distance were assessed to  
143 remove any influential observation originating from studies marked as having potential-for-  
144 bias. Publication bias was assessed by funnel plots and statistical tests investigating the  
145 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 ( $\tau^2$ ), 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,

199 intestinal disorders, alcoholism, autoimmune disease, and blood disorder) had also  
200 significantly higher odds of acquiring salmonellosis (pooled OR=3.289 95% CI [2.449 -  
201 4.416]). The same level of odds was observed in patients receiving other medications, such  
202 as NSAID, corticosteroids, thyroid and hormone drugs (pooled OR=4.655 95% CI [3.458 -  
203 6.266]). When focusing on children, the use of anti-acids (pooled OR=3.413 95% CI [1.851 -  
204 6.296]) and antibiotics (pooled OR=2.376 95% CI [1.618 - 3.489]) produced a similar degree  
205 of salmonellosis risk. In the population of infants, breastfeeding was proven to be protective  
206 against *Salmonella* infection. Combining the results from seven case-control studies, 747  
207 infants of age lower than 2 years had a pooled OR of 0.249 95% CI [0.165 -0.377] times the  
208 odds of becoming ill than those who were not breastfed.

209 Person-to-person transmission was a significant risk factor for both the mixed population and  
210 children, but it was much higher in the latter, with a pooled OR of 1.692 95% CI [1.145 -  
211 2.500] and 3.811 [1.977 - 7.348], respectively. Person-to-person transmission was described  
212 in the mixed population as contact with patient or contact household member with diarrhea  
213 (or confirmed cases). For the **child population**, contacts were described as contact with  
214 diarrhea in household or creche with an ill child.

215 Contact with animals (farm, pet or wild) for children as well as in the mixed population was an  
216 exposure pathway widely explored in the different studies (127 ORs for 30 studies in the  
217 mixed population, and 44 ORs from 9 studies for children). In the mixed population, the  
218 pooled ORs for this route of exposure ranged from 1.471 to 2.619 (contact with pets, on-farm  
219 activities, or professional activities related to animals and carcasses, and contact with wild  
220 animals). Farm environment was also found to be a risk factor in the mixed population  
221 (pooled OR 1.900 95% CI [1.251 - 2.885]). For children, the pooled ORs associated with  
222 contact with pets and farm animals were 3.035 95% CI [1.938 - 4.756] and 2.658 95% CI  
223 [1.431 - 4.938], respectively. When exploring in more detail the pet factor, for both  
224 populations, the diversity of animals was important (reptiles, dogs, cats, pets with diarrhea,  
225 etc.). The categories of farm animals and wild animals were also very diverse.

226 For the mixed population, salmonellosis cases occurred more frequently among people  
227 exposed to water-related activities (fishing, swimming, sailing, etc.) (pooled OR=2.221 95%  
228 CI [1.339 - 3.681]). Drinking water practice was also significantly associated with increased  
229 salmonellosis risk. Within this category, the consumption of untreated water was associated  
230 with salmonellosis for the mixed population (pooled OR=1.753 95% CI [1.109 - 2.770]) and  
231 represented a risk factor specifically for children too (pooled OR=2.130 95% CI [1.285 -  
232 3.532]) (Figure 2). For children, outdoor activities (activities in parks, playground sandboxes,  
233 contact with soil, etc.) were strongly associated with salmonellosis (pooled OR=3.055 95% CI  
234 [2.243 - 4.160]). Childcare attendance was significantly associated with salmonellosis  
235 (pooled OR=2.738 95% CI [2.243 - 4.160]) in children, but strength or ORs were very  
236 different in different childcare settings (e.g. school, daycare).

### 237 **Significant risk factors associated with food-related transmission pathways**

238 Significant factors associated with food are given in Tables 1, 2 and 3. The studies explored  
239 a wide range of foods and food preparation/consumption practices (e.g. hygiene, cooking,  
240 and place of consumption). For the mixed population foods significantly associated with  
241 salmonellosis were eggs and egg products (pooled OR=1.774 95% CI [1.351 - 2.329]),  
242 composite foods (pooled OR=1.731 95% CI [1.258 -2.381]), and meat (pooled OR=1.489  
243 95% CI [1.137 - 1.951]) (Table 1). Within eggs category, higher pooled OR values were  
244 obtained for egg products (pooled OR=2.736 95% CI [1.502 - 4.987]) compared to eggs  
245 (pooled OR= 1.976 95% CI [1.138 - 3.431]).

246 Among meats, poultry (pooled OR=1.474 95% CI [1.167 - 1.861]), pork (pooled OR=1.563  
247 95% CI [1.111 - 2.200]), red meats other than beef (pooled OR=1.680 95% CI [1.044 -  
248 2.703])(as lamb, mutton or venison meat), and other meats (pooled OR = 1.938 95%CI  
249 [1.215 - 3.091]) were the most important risk factors in the mixed population (Table 2).The  
250 category “others” is very heterogeneous containing meats of non-specified origin. The food  
251 vehicles identified in children also comprised meat and eggs categories (Table 1). For meat  
252 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.

## 273 **Discussion**

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

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

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

297 The food risk factors identified in the meta-analysis were corroborated by the analysis of  
298 epidemiological data. Consumption of raw eggs, undercooked pork, poultry, beef, and milk  
299 formula regularly cause outbreaks (Guillier et al., 2013; Dallman et al., 2016; Jones et al.,  
300 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

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

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

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

## 354 **Conclusion**

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

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

365

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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**

573 **Figure captions**

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

576

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

580

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

583

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

587

588

590 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***
<b>Travel</b>								
<b>Mixed(y)</b>	Asia excluded	Abroad	3.612 [2.839 - 4.593]	18/47	<.0001	0.408	1	τ <sup>2</sup> =0.0624 QE(df = 49) = 123.6, p-val < .0001 s <sup>2</sup> =0.925 ; I <sup>2</sup> =6.319%
		Inside	2.195 [1.054 - 4.572]	3/3	0.036			
<b>Host specific</b>								
<b>Mixed(y)</b>	All	Antiacids	3.184 [2.449 - 4.139]	12/31	<.0001	<.0001	0	τ <sup>2</sup> =0.6956 QE(df = 88) = 866.970, p-val < .0001 s <sup>2</sup> =0.533; I <sup>2</sup> =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			
<b>Children</b>	All	Antiacids	3.413 [1.851 - 6.296]	2/3	<.0001	0.501	0	τ <sup>2</sup> =0.278 QE(df = 24) = 31.053, p-val = 0.152 s <sup>2</sup> =0.500; I <sup>2</sup> =35.724%
		Antibiotics	2.376 [1.618 - 3.489]	6/12	<.0001			
		Breastfeeding	0.249 [0.165 - 0.377]	7/12	<.0001			
<b>Person to person</b>								
<b>Mixed</b>	All		1.692 [1.145 - 2.500]	7/10	0.008	0.056	0	τ <sup>2</sup> =0.557 QE(df = 17) = 58.734, p-val < .0001 ; s <sup>2</sup> =0.82; I <sup>2</sup> =40.425%
<b>Children</b>			3.811 [1.977 - 7.348]	7/9	<.0001			
<b>Animals</b>								
<b>Mixed</b>	All	Pets	1.471 [1.189 - 1.821]	26/71	<.0001	0.283	1	τ <sup>2</sup> =1.1449 QE(df = 123) = 464.3872, p-val < .0001 ; s <sup>2</sup> =0.605; I <sup>2</sup> =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			
<b>Children</b>	All	Pets	3.035 [1.938 - 4.756]	9/36	<.0001	0.731	1	τ <sup>2</sup> =0.369 QE(df = 41) = 76.2961, p-val = 0.0007; s <sup>2</sup> =0.540; I <sup>2</sup> =40.63%
		Farm animals	2.658 [1.431 - 4.938]	2/5	0.002			
<b>Environment</b>								
<b>Mixed</b>	All	Recreational water	2.221 [1.339 - 3.681]	9/12	0.0020	0.088	0	τ <sup>2</sup> =0.7714 QE(df = 45) = 132.6221, p-val < .0001; s <sup>2</sup> =0.594; I <sup>2</sup> =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			
<b>Children (at)</b>	All	Untreated drinking water	2.130 [1.285 - 3.532]	5/8	0.0034	0.199	0	τ <sup>2</sup> = 0 QE(df = 27) = 31.5105, p-val = 0.2507 ;s <sup>2</sup> =0.431 I <sup>2</sup> = 0
		Daycare attendance	2.738 [1.658 - 4.522]	5/10	<.0001			

		Playground	3.055 [2.243 - 4.160]	6/13	<.0001			
<b>Food</b>								
<b>Mixed</b>	<b>All</b>	Meat	1.489 [1.137 - 1.951]	37/231	0.0039	0.035	8	τ <sup>2</sup> =0.215 QE(df = 537) = 1971.5989, p- val < .0001 ; s <sup>2</sup> =0.792; I <sup>2</sup> =21.34%
		Eggs	1.774 [1.351 - 2.329]	35/139	<.0001			
		Composite	1.731 [1.258 - 2.381]	16/66	0.0008			
<b>Children</b>	<b>All</b>	Meat	1.794[1.548 - 2.079]	8/34	<.0001	0.072	2	τ <sup>2</sup> = 0.6705 QE(df = 76) = 93.1415, p-val = 0.0884 s <sup>2</sup> =0.482 ; I <sup>2</sup> =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			

591

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

596

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***
<b>Meat</b>	Mixed	Asia and south America removed	Poultry	1.474[1.167 - 1.861]	29/93	0.0011	0.202	2	$\tau^2=1.93$ 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			
<b>Meat (y)</b>	Children	All	Beef	1.623 [1.072 - 2.473]	5/12	0.022	0.117	0	$\tau^2=0.567$ 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			
<b>Eggs (at,y)</b>	Mixed	Asia and south America removed	Eggs	1.976[1.138 - 3.431]	32/115	0.0155	0.592	0	$\tau^2= 0.219$ 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			
<b>Eggs (at)</b>	Children	All	Multivariate analysis	1.557 [1.233 - 1.967]	3/5	0.0002	0.915	0	$\tau^2=0$ 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			
<b>Dairy</b>	Children	All	Milk formula	3.324 [2.136 - 5.172]	5/8	<.0001	0.014	0	$\tau^2=0.111$ Q(df = 7) = 9.665, p-val = 0.208 $s^2=0.22810$ $I^2 : 0.228$
<b>Produce</b>	Children	All		1.545 [1.314 - 1.819]	2/10	<.0001	0.535	0	$\tau^2=0$ Q(df = 9) = 8.4746, p-val = 0.4871 $s^2=0.805$ ; $I^2=0$
<b>Composite</b>	Children+mixed (all)	Asia removed	Dishes	1.609 [1.206 - 2.147]	16/46	0.0012	0.121	0	$\tau^2=0.742$ 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			
<b>BBQ</b>	All	All		1.952 [1.003 - 3.798]	4/7	0.0491	0.221	0	$\tau^2=0.274$ Q(df = 6) = 15.967, p-val = 0.0139 $s^2=0.669$ ; $I^2=29.059\%$

598 \*N/n Number of studies/number of OR;\*\* points removed by sensitivity analysis, all results are given  
599 after removing data concerned; \*\*\*Between-study variability ( $\tau^2$ ), test for residual heterogeneity (QE),  
600 variance of residuals ( $s^2$ ), intra-class correlation ( $I^2$ ). (y): year is significant (before/after 2000) in this  
601 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***
<b>Poultry (at)</b>	Eating Out	3.038 [1.965 - 4.697]	<b>12/24</b>	<.0001	1.961 [1.583- 2.429]	<b>3</b>	0.032	$\tau^2=0.124$ QE(df = 102) = 243.7902, p-val < .0001 $s^2=0.593$ ; $I^2=17.311\%$
	Undercooked	3.986 [1.641 - 9.681]	<b>6/8</b>	0.0054	2.572 [1.322 - 5.005]			
	Poultry (base)	1.549 [1.241 - 1.934]	<b>32/82 (ref eating out)</b> <b>34/98 (ref handling)</b>	0.0001	-			
<b>Processed Meat</b>	Eating out	1.919 [0.922 - 3.994]	<b>7/13</b>	0.021	1.635 [1.074 - 2.487]	<b>2</b>	0.009	$\tau^2=0.303$ 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]	<b>17/48</b>	0.315	-			
<b>Eggs (at)</b>	Eating Out	2.575 [1.465 - 4.527]	<b>10/29</b>	0.0011	1.575 [1.199 - 2.069]	<b>3</b>	0.787	$\tau^2=0.174$ QE(df = 135) = 423.730, p-val < .0001 $s^2=0.818$ $I^2=17.574\%$
	Undercooked	2.182 [1.388 - 3.428]	<b>22/49</b>	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	-			
<b>Pork meat</b>	Undercooked	3.039 [1.289 - 7.163]	5/12	<.0001	3.578 [2.132- 6.002]	0	p= 0.259	$\tau^2=0.1051$ 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	-			
<b>Vegetables</b>	Unwashed	1.542 [0.773- 3.073]	2/4	0.112	1.551 [1.002 - 2.399]	0	p= 0.378	$\tau^2=0.136$ 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 ( $\tau^2$ ), 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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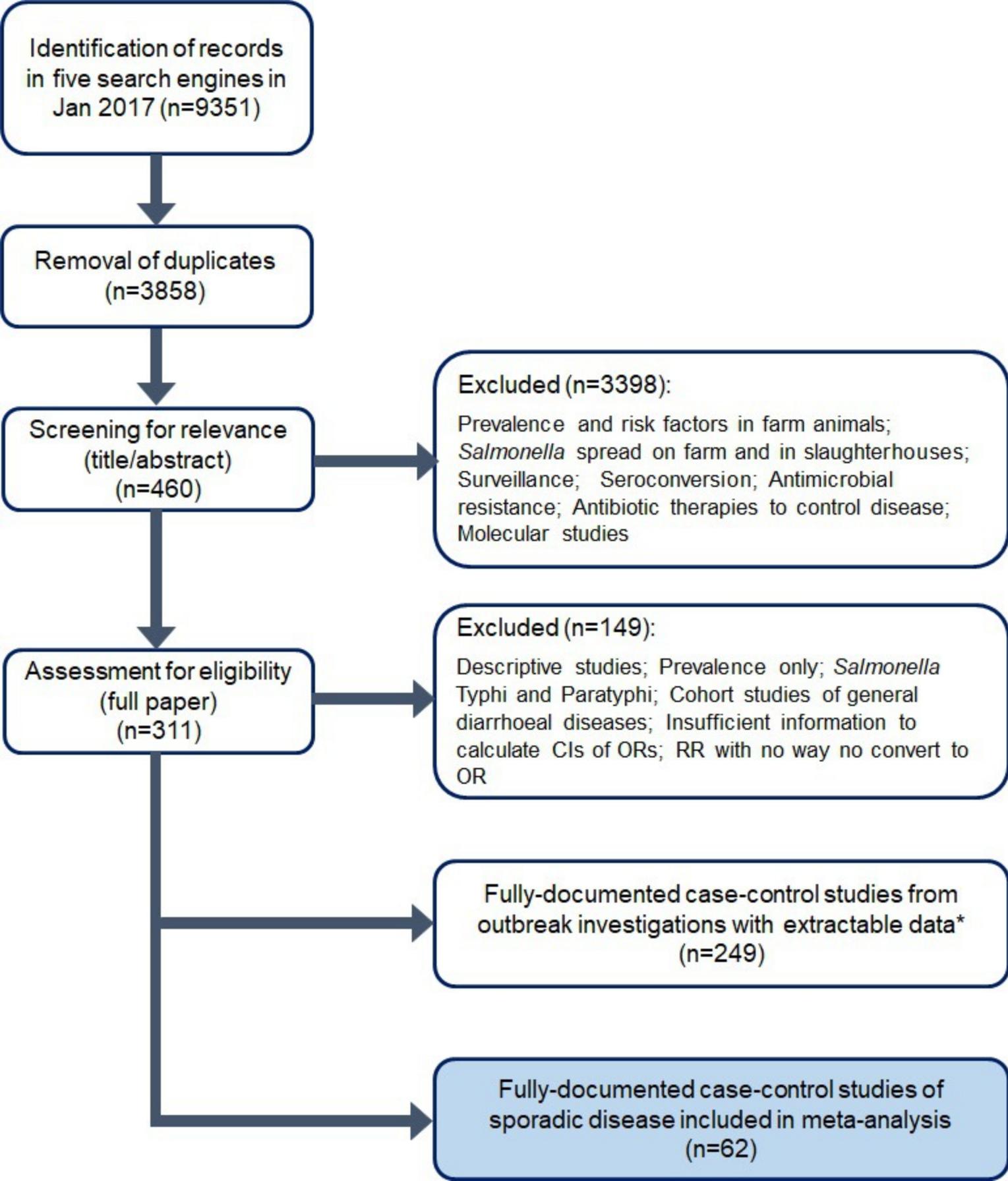
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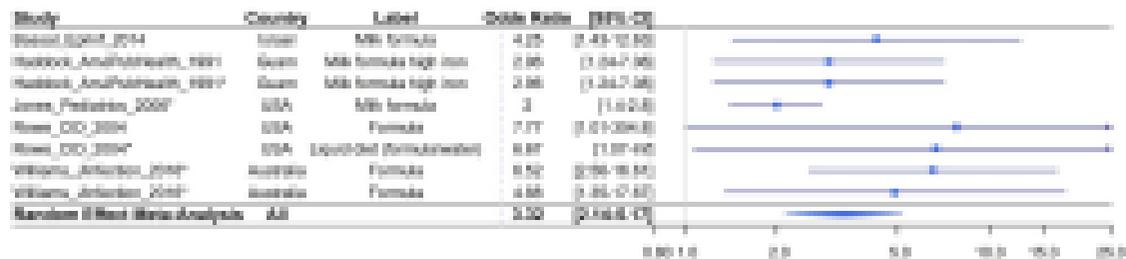
611 Table 4. Non significant or isolated *ORs* (1 publication) in main risk factors.

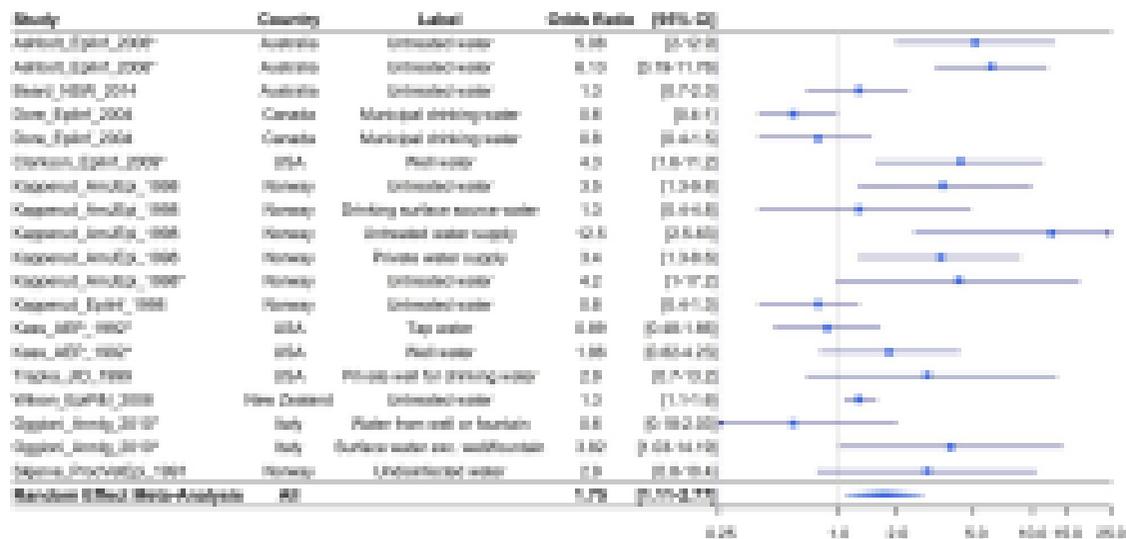
Population	Geographical area	Risk factor	Pooled OR [IC95%]	N/n*
<b>Travel</b>				
<b>Mixed(y)</b>	Asia excluded	Any	0.909[ 0.528- 1.565]	<b>2/3</b>
<b>Animals</b>				
<b>Children</b>	<b>All</b>	Exotic (new) pets	1.433[ 1.046- 1.962]	1/3
<b>Food</b>				
<b>Mixed</b>	<b>All</b>	Produce	1.228[ 0.892- 1.690]	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
<b>Children</b>	<b>All</b>	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

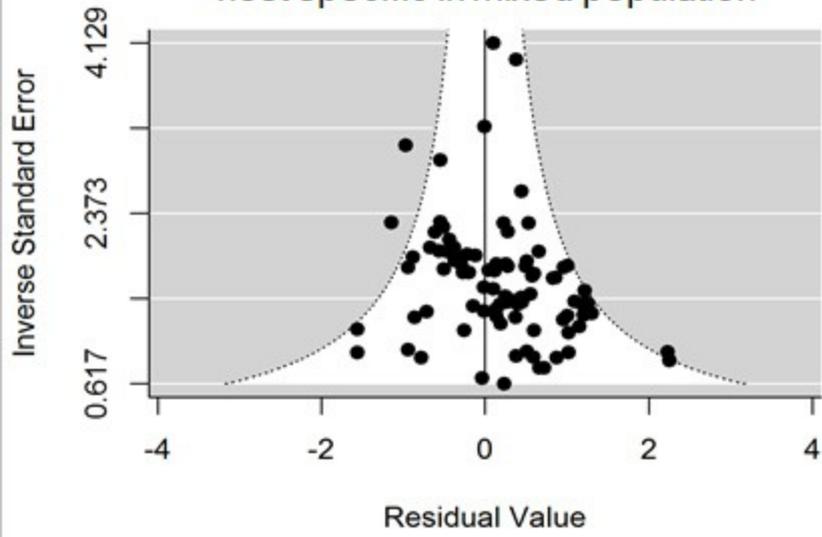
613 due to the lack of studies



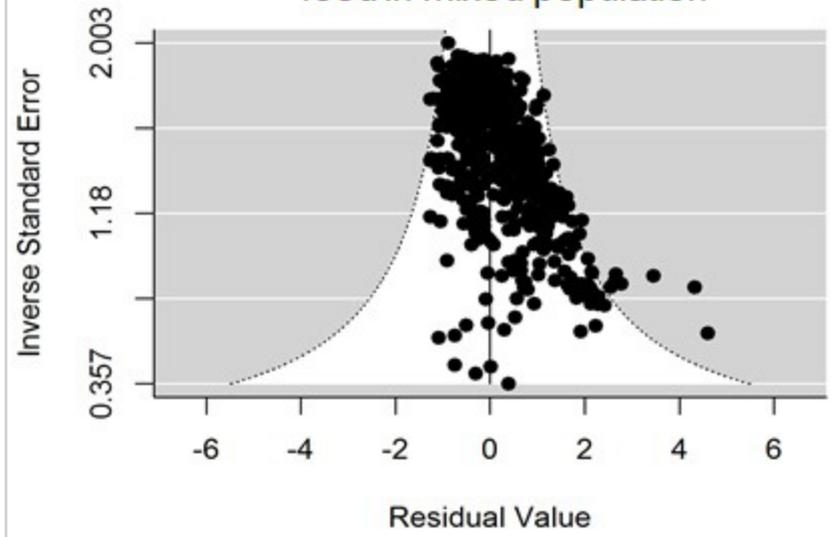




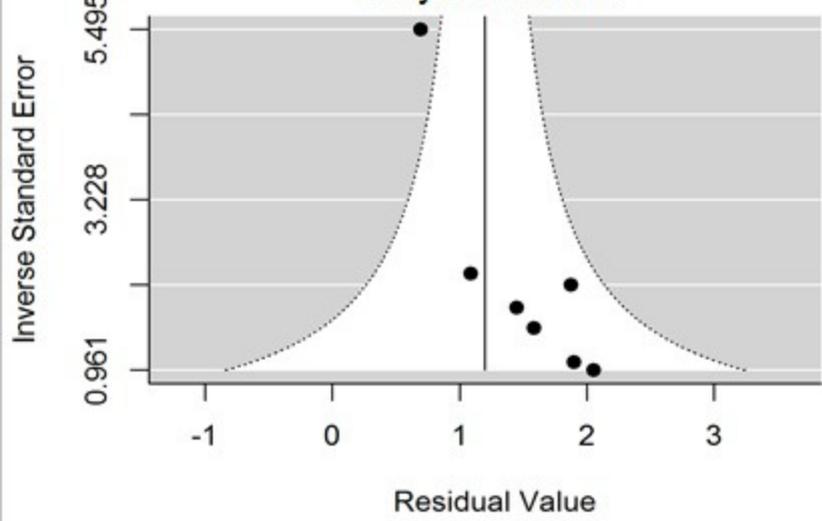
host specific in mixed population



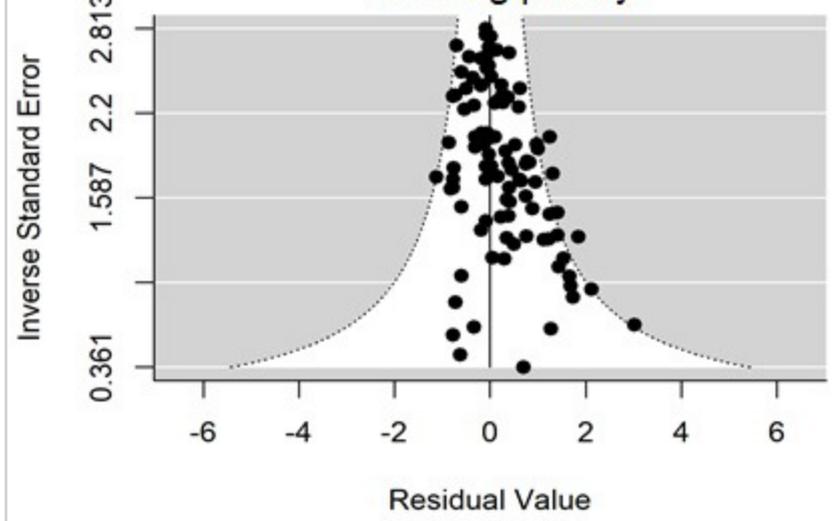
food in mixed population



dairy in children



handling poultry



handling processed meat

