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Authors

Anne Thébault¹, Julie David², Pauline Kooh¹, Vasco Cadavez³, Ursula Gonzales-Barron³, Nicole Pavio⁴

Affiliations

1. Risk assessment Department, French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Maisons-Alfort, France
2. ANSES, Ploufragan-Plouzané laboratory, Ploufragan, France
3. Centro de Investigação de Montanha – (CIMO), Instituto Politécnico de Bragança, Bragança, Portugal
4. ANSES, Animal Health Laboratory, UMR 1161 VIROLOGIE INRA, ENVA, Maisons-Alfort, France

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

Short Title

Meta-analysis on risk factors associated to norovirus infection

Highlights

- The study of sporadic norovirus cases remains poorly documented
- Results of meta-analysis confirm the major role of inter-human transmissions
- Environment, seafood and composite foods are risk factors of norovirus infection
- Lack of standardized definition of sporadic infection of norovirus
- Too broad definition of exposure limits the interpretation

Keywords

Research synthesis; meta-regression; case-control studies; Norovirus; odds-ratio

Abstract

Norovirus is responsible for 20% of acute gastroenteritis worldwide. The fecal-oral route of transmission is known, but we proposed a first attempt to identify the relative importance of different sources and vehicles for sporadic cases using meta-analysis models. Case-control and cohort/cross-sectional studies were systematically reviewed and analyzed to assess the main risk factors associated with sporadic norovirus infections. Suitable scientific articles were identified through systematic literature search and subjected to a methodological quality assessment. Mixed-effects meta-analyses models were adjusted by population type to appropriate risk factor categories. The quality assessment stage led to include 14 primary studies conducted between 1993 and 2014. From these, eight studies investigated exposures in children/infants, and eight concerned the mixed population.

The meta-analysis confirmed the oro-fecal route for norovirus infections, with the person-to-person transmission (pooled OR=3.002; 95% CI: [2.502 -3.060] in mixed population), and the lack of personal hygiene (pooled OR=2.329; 95% CI: [1.048 -5.169]). The meta-analysis also enlightened the role of indirect transmission through the environment with pathways like untreated drinking water (mixed population), with a pooled OR=2.680 (95% CI: [1.081-

35 6.643]) and farm environment (children population). Indirect transmission also involved the
36 food pathway, which was finally found significant with consumption of seafood (mixed
37 population) (pooled OR=2.270; 95% CI: [1.299-3.968]) and composite food (eating
38 outside/uncooked mixed and young population) (pooled OR=4.541; 95% CI: [3.461-5.958]).

39 These results are coherent with the findings from studies on outbreaks.

40 . However, a too broad definition of exposure factors limited the interpretation of results, as
41 occurred with the seafood pathways that combined fish and shellfish. Other factors such as
42 consumption of Food-handled products or the type of drinking water deserve to be better
43 investigated. Furthermore, better harmonization in case definition and appropriate case-
44 control or cross-sectional studies would allow better addressing sporadic cases risk factors,
45 especially for susceptible populations, such as children, elderly or immunosuppressed
46 persons.

47

48

49 1. Introduction

50

51 Norovirus is estimated to contribute to 20% acute gastroenteritis worldwide (Ahmed et al.,
52 2014). In USA, Japan, and Europe, around 50% of all outbreaks of gastroenteritis are
53 attributed to norovirus (Patel et al., 2009). The peak of norovirus disease outbreaks usually
54 occurs in temperate developed countries during wintertime (Mounts et al., 2000).

55 Norovirus infection is characterized by a short incubation of 24-48 hours (Karst et al., 2010).
56 Symptoms usually described are sudden onset of severe vomiting (originally called ‘winter
57 vomiting disease’), abdominal cramps, myalgia, and non-bloody-diarrhea, usually resolving
58 in 2-3 days (Karst et al., 2010). In high-risk groups such as young children, elderly, and
59 immunodeficient people, severe symptoms can lead to dehydration and hospitalization or
60 even death (Karst, 2010; Verhoef et al., 2013; Green et al., 2014). Among patients
61 hospitalized for severe gastroenteritis, norovirus infections account for around 12% of cases
62 among children below 5 years old. It is the second cause of endemic diarrhea in children
63 worldwide after rotavirus infections (Patel et al., 2009).

64

65 The norovirus genus belongs to the *Caliciviridae* family. This genus is divided into ten
66 genogroups (GI to GX) and 49 genotypes (Chhabra et al. 2019). Norovirus canes infect
67 humans and mammalian animals, but no zoonotic transmission has been described (De Graaf
68 et al.,2016). Within each genogroup, different genotypes are described and can be subdivided

69 into strains or variants Novel variants can emerge periodically, such as GII. 4 (Sydney) or
70 GII.7 (Atmar et al., 2018). The mutation rate is high, and the diversity of strains is of
71 importance for explaining escaping immunity and regular epidemics in human populations
72 (Dingle *et al.*, 2004; Lindesmith *et al.*, 2008; Bull *et al.*, 2010). Humans are the reservoir for
73 human norovirus strains. During outbreaks, common routes of transmission are person-to-
74 person contact and food contaminated by infectious food-handlers, such as ready-to-eat foods
75 that require human handling, and that are consumed without further cooking (Guix et al.,
76 2019). Different food products were also identified as the origin of outbreaks after indirect
77 contamination with human fecal matter. For example, shellfish harvested in marine
78 contaminated waters (Maalouf et al., 2010) and vegetables, soft fruit such as raspberries or
79 leafy greens (salads) irrigated with water contaminated by sewage (Muller et al, 2016;
80 Tavoshi et al., 2015).

81
82 Methods for norovirus genome detection are available for clinical and environmental samples,
83 such as water, or food, like shellfish. Protocols using molecular tools have been developed
84 (RT-PCR, real-time RT-PCR and digital-real time RT-PCR) (Polo et al., 2016), but these
85 rapid and accurate diagnostic assays remain costly for developing countries. Besides,
86 molecular tools are not able to differentiate between infectious and non-infectious viruses,
87 even now that a new approach to solve this issue is promising (Manuel et al., 2018; Chan et
88 al., 2019).

89 Risk attribution for sporadic cases of norovirus infection remains a challenge by risk
90 assessment approach -due to uncertain estimates of infectious viral contamination, and
91 epidemiological data appear more reliable. Given the globalization of the food chain, it is
92 important to investigate sporadic cases at a global scale . Hence, the objective of this study
93 was to assess risk factors for norovirus sporadic infection by systematic review and meta-
94 analysis of case-control studies, regardless of the country of origin. However geographical
95 differences, if detected, can be further analyzed and discussed.

96

97 **2. Material and methods**

98

99 To determine the main risk factors for sporadic norovirus cases, relevant scientific
100 information contained in epidemiologic case-control and cross-sectional/cohort studies
101 publications has been systematically reviewed. The protocol of the systematic review and the

102 meta-analysis model are described in depth in the methodological article of this special issue
103 (Gonzales-Barron et al., 2019).

104

105 **2.1 Systematic review**

106 The Literature search was conducted from March 2017 to December 2017 using a
107 combination of keywords related to (1) Norovirus OR Norwalk, (2) case-control OR risk
108 factor OR cohort, and (3) infection OR disease, joined by the logical connector AND.
109 Relevant studies were identified from five bibliographic search engines, Science Direct,
110 PubMed, Scielo, ISI Web of Science and Scopus. . The search was limited to the languages
111 English, French, Portuguese and Spanish. No restrictions were defined for the year of the
112 study or type of publication. Each reference record was screened for relevance for inclusion in
113 the meta-analysis study, and subsequently, the methodological quality of the “candidate”
114 studies were assessed using pre-set quality criteria comprising (1) appropriate selection of the
115 controls; (2) adjustment to correct for confounders, (3) comparability between cases and
116 controls, (4) acceptable responses rates for the exposed and control groups; (5) Data analysis
117 appropriate to the study design; (6) provision of Odd ratio (OR) with confidence interval or p-
118 value; or provision of sufficient data to calculate ORs; overall quality of the study (Gonzales-
119 Barron et al., 2019).

120 Primary studies that passed the screening for relevance were marked as having potential for
121 bias if they failed to meet at least one of the methodological quality assessment criteria (Table
122 1). Data from primary studies were then extracted using a standardised spreadsheet. Data
123 extracted included the relevant study characteristics (location, time period, population, case
124 definition, design, sample size of the groups, type of model, etc.), the risk factors, the setting,
125 the handling practices and the outcome of the study (OR).

126

127 **2.2 Data synthesis**

128 The joint meta-analytical data was first described using basic statistics. Next, data was
129 partitioned into subsets of categories of risk factors: travel, host-specific factors and
130 transmission pathways related to person-to-person contagion, animal contact, environmental
131 exposures and food vehicles. The variable population was stratified into mixed (adults or
132 undefined) and children (at least under 16 years old). Meta-analysis models were then fitted to
133 each of the data subsets in order to estimate the overall ORs associated to the risk factors. The
134 meta-analytical models were fitted separately by population type. The statistical analysis was
135 designed to assess the effect of the geographical region. The objective of the region-specific meta-

136 analysis was to inform the decision on the geographical regions that should be kept for the
137 subsequent pooling of ORs. A Geographical region (Asia, North America, South America, Africa,
138 Europe, Oceania) was removed from a particular meta-analysis partition only if its pooled ORs were
139 different from those associated with the other regions or if less than 3 ORs represented the region
140 (Gonzales-Barron et al., 2019). The situation of exclusion of a particular region never occurs for
141 norovirus, because no strong heterogeneity between regions was detected (when this analysis
142 was feasible).

143 Even if no heterogeneity between regions is detected, meta-analytical forest plots constructed
144 for all risk factors provide information about heterogeneity between studies, the precise risk
145 factor label applied in each study and in particular the period and country of origin of the
146 study.

147 All meta-analysis models were essentially weighted random-effects linear regression models.
148 Each category (i. e travel) is investigated with meta-regression for subcategory (e.g. abroad, inside)
149 (Gonzales-Barron et al., 2019). Once a meta-analysis model was fitted, influential diagnostics
150 statistics were assessed in order to remove any influential observation originating from studies
151 marked as having potential-for-bias. Publication bias was assessed by funnel plots, exploring the
152 relationship between the observed outcome (or residuals of the model with moderators) with their
153 corresponding inverse standard error (Gonzales-Barron et al., 2019).

154 Next, a Statistical test investigates the effect of the study sample size on the ORs, which is expected
155 to be non significant (Table 3) (Gonzales-Barron et al., 2019). Heterogeneity between studies was
156 assessed by different indicators such as the between-study variability (τ^2), the QE test investigating
157 residual heterogeneity, the variance of residuals and the intra-class correlation I^2 (Gonzales-Barron et
158 al., 2019).

159
160). All analyses were produced using the R software (R Development Core Team, 2008)
161 implemented with the metafor package (Viechtbauer, 2010). The meta-analyzed risk factors
162 are presented in Table 3 only when significant. Pooled ORs were considered as significant
163 when the lower bound of the 95% CI was equal or greater than 1.). Whenever a category is s
164 not significant, the result is given in Table 4.

165 **Results**

166

167 **3.1 Descriptive statistics**

168 In the systematic review of risk factors pertaining to human infection with norovirus, a total
169 of 672 bibliographic sources were identified using the keywords in the five search engines,

170 from which 99 of those passed the full assessment for eligibility, comprising case-control and
171 cohort studies from both sporadic illnesses and outbreaks (Figure 1). Eighty-five fully-
172 documented case-control studies investigated the source(s) of outbreaks and excluded. The
173 overall exclusion process is described in methodological paper (Gonzalez-Barron et al.,
174 2019). Meta-analysis was undertaken using 14 primary studies – case-control and cohort
175 studies – with focus on sporadic disease, conducted between 1993 and 2013 (Table 1).
176 Among those 14, six studies were done after 2009, 11 after 2000, and by decreasing order
177 they come from Western Europe (6), Asia (4) and the other ones from another part of Europe
178 (2), North America (1) and Latin America (1). The eligible studies jointly provided 102 odds-
179 ratios associated with risk factors that were categorized for meta-analysis. A total of 54 ORs
180 were retrieved from 3 case-control studies performed before the year 2000, while 48 ORs
181 were extracted from 11 studies performed after 2000. Meta-analytical data were obtained
182 from studies conducted in 10 countries: 83% of the ORs originate from 5 countries only, the
183 Netherlands (35 ORs), UK (19 ORs), Vietnam (13 ORs), China (9 ORs) and Mexico (9 ORs).
184 Ten primary studies employed an unmatched experimental design, from them three did not
185 adjust ORs by any confounder (i.e., crude ORs by Chi-square test), while the others were
186 adjusted for other factors by using unconditional logistic regression. Four studies employed a
187 matched experimental design. Most of them were adjusted ORs estimated by logistic
188 regressions (Table 1).

189

190 The population is divided in adults or mixed population (50 ORs in 9 publications) and
191 children (52 ORs in 8 publications) (Table 1). Risk factors categories studied were, in
192 decreasing order, transmission from person-to-person (38 ORs) (e.g. contacts with person
193 with diarrhea), food (28 ORs) (e.g. eating shellfish), environment (18 ORs)(e.g. living in rural
194 residence, drinking well water), host specific (hygiene included) (9 ORs)(e.g.
195 immunosuppression), contact with animals (7 ORs) (e.g. contact with pets, livestock or
196 poultry) and travel (2 ORs). Two publications had potential bias (Table 1): In Enserink et al
197 (2015), the publication gives estimated IRR (incidence rate ratios) that were assumed to be
198 close to OR (3 ORs in the category environment). The second one addresses cases with
199 prolonged norovirus excretion (>10 days) in comparison of cases with short excretion
200 (Henke-Jendo, 2009) (6 ORs concerning different host factors). Few papers mentioned clearly
201 the genogroup (6 papers), some of them mentioned mixed genogroups (GI/GII) (3), one GI or
202 GII and three genogroup GII.4. No particular link between genogroups and risk factors could
203 be evidenced.

204

205 Even if the definition of case of acute gastroenteritis associated with norovirus infection was
206 slightly different between studies either in the definition of the controls or in the detection
207 method, still all of them were included. For some studies, the ORs were based only on
208 norovirus detection (Table 2), while, in others, the definition includes acute gastroenteritis
209 with evidence of norovirus infection. This discrepancy was also described in the meta-
210 analysis by Ahmed et al. (2014). We assumed that risk factors of infection could be
211 extrapolated to norovirus gastroenteritis. The criteria for cases recruitment were various,
212 ranging from recruitment at hospitals to the general population (Table 2), therefore probably
213 including different severity of cases or age for children (Table 2). We assumed that the
214 severity of the disease did not influence the significance of risk factors.

215

216 3.2 Meta-analysis results

217 All significant results are given in Table 3. Travel exposure could not be included in the meta-
218 analysis due to scarcity of data (2 ORs extracted from one study in England: Phillips et al.,
219 2010). In this study, international travel was evaluated as risk factor for acquiring norovirus
220 infection in both children and mixed population. Likely, host-specific factors, such as
221 suffering from a chronic disease (e.g., immunosuppression) or another medical condition
222 (e.g., being a transplant recipient), were investigated in only one study with 6 ORs (Henke-
223 Gendo, 2009), and hence, they were excluded from the meta-analysis.

224

225 The contact, at home or outside home, with an ill person suspected or known to have
226 norovirus was studied in 6 publications (38 ORs). Adults who have contact with infected
227 persons, within or outside the household, presented a pooled OR of 3.002 (95% CI: [2.502 -
228 3.602]; Table 3). The pooled OR of person-to-person transmission for children was also
229 significant (pooled OR=4.648; 95% CI: [2.092 – 10.33]), and higher than that of the mixed
230 population. The details of the ORs for person-to-person transmission in log scale are given in
231 Figure 2 for children, and in Figure 3 for mixed population. Diversities of contacts with ill
232 person or household members with gastroenteritis, or vomiting, are described inside
233 household, or outside (Figure 2 and 3). Lack of handwashing (after toilets) was studied in
234 children and was shown to be a significant with a pooled OR=2.329 (95% CI: [1.049 -
235 5.169]), but with only 2 ORs from 2 publications.

236

237 The environmental pathways in mixed population included farm environment, attendance to
238 daycare center, and drinking water. The first two routes could not be analyzed since they only
239 consisted of only one OR each. Drinking water was not found significant in the mixed
240 population with a pooled OR=1.753 (95% CI: [0.969 - 3.171]; Table 4). Nonetheless,
241 excluding 2 ORs coming from “tap water”, therefore restricting analysis to non-treated
242 drinking water such as “local water supply” and “spring water”, produced a significant pooled
243 OR of 2.680 (95% CI: [1.081 - 6.643]).

244

245 For children, attending daycare (2 publications, 3 OR) was not found significant with one
246 publication from Vietnam (lower OR) and the other one from the Netherlands (higher ORs).
247 Drinking water from wells or other sources was not found significant in children, although the
248 information was too limited (1 publication from My et al, 2013 with 4 ORs). Playing in a
249 padding pool or sandpit was only represented by one OR, and was hence removed from the
250 analysis. The children population exposed to rural conditions of living (living on a farm)
251 clearly showed a significant pooled OR (1.563; 95% CI: [1.082 - 2.258]). Contact with
252 animals (cats, dog, bird, livestock,) was studied as a potential route in five publications (7
253 ORs) for both mixed and children population, but it was not found to be a significant factor
254 (pooled OR=1.198; 95%: [0.558 - 2.577]).

255

256 For the mixed population, different food products were scrutinized in several papers (8 ORs in
257 4 publications), such as vegetables (2 ORs), mineral water (1 OR), sweet beverages (1 OR),
258 shellfish (2 ORs), fish (1 OR) or “suspicious food” (1 OR). Due to the low number of ORs in
259 each category, only 3 subcategories were investigated. While seafood was found significant
260 (OR=2.270; 95% CI: [1.299 - 3.968] in Table 3), neither beverages (1 publication, Fretz
261 (2005)) nor crop produces (1 publication, Fretz (2005)) were found significant and hereafter
262 could not be proven as important vehicles for norovirus transmission. For seafood, it is worth
263 mentioning that in the UK the consumption of oysters (OR=18.30; 95% CI: [1.50 – 223.30])
264 and whelks and winkles (OR=20.50; 95% CI: [1.60 – 262.6]) bore higher risk of disease than
265 the consumption of fish in the Netherlands (OR=1.80; 95% CI: [1.00 – 3.24]).

266

267 For children, 14 ORs in 3 publications describe different food items (Dai et al., 2010; My et
268 al., 2013; Peasey et al., 2004). In China and Vietnam, data were available about consumptions
269 in market food (2 ORs), eating outside (1 OR), uncooked food (2 ORs), seafood (1 OR),
270 bottled water (2 ORs). In Mexico, different ways of chicken or meat consumption were

271 investigated (6 ORs). Then, two categories of food products could be investigated: a
272 composite category and meat. Consumption of composite food was found highly significant
273 (OR=4.541; 95% CI: [3.461-5.958]). However, this category is heterogeneous with details
274 given in Figure 4. In any case, it can be observed that eating uncooked, outside, or in market
275 food can be at risk for children consumers in China and Vietnam. For meat, all ORs came
276 from the same publication (Peasey et al., 2004), and the pooled OR was not found significant.

277
278 For all the meta-analytical models reported in Table 3, the statistical tests indicated the
279 presence of potential significant publication bias below 5%, with exception of no
280 handwashing, person-to-person transmission, and environment and food in children. For
281 better assessing the publication bias, the funnel plots for models with significant publication
282 bias are given in Figure 5 “No handwashing” has too few ORs to be taken into consideration.
283 For “person-to-person” and “environment” in children population, there was an asymmetry
284 towards lack of small studies with smaller ORs. Furthermore, since there were very few ORs
285 for food products in the mixed population, an overall trend in the funnel plot is not obvious,
286 and is probably linked to the heterogeneity in the different kind of food products in this
287 category. Moreover, the intra-class correlation, as percentage of the total variance that is
288 explained by the variation between studies, “I²”, was always below high heterogeneity
289 (<75%) (Table 1). Most often, remaining between-study heterogeneity (significant p-val
290 below 0.05 for Q or QE) was not observed for the data partitions, except for person-to-person
291 transmission.

292 293 **3. Discussion**

294 The main results of this meta-analysis on norovirus sporadic cases are in agreement with the
295 global feco-oral pathway for norovirus transmission. Person-to-person contact was identified
296 as the major risk factor, involving mechanical transmission from environmental surfaces,
297 hand contacts or vomit aerosols. Outbreaks data are in line with these results, since they have
298 been described in closed environments, such as elementary schools, hospitals, day-care
299 centers, cruise ships or military settings, and favored by person-to-person contact, either direct
300 or secondary (Ho et al., 1989; Loury et al., 2012; Sukrie et al., 2012; Patel, 2009; Karst,
301 2010). Lack of hygiene, namely “no handwashing after using the toilet”, was found to be a
302 significant risk factor in this meta-analysis, probably linked to an indirect inter-human
303 transmission. Washing hands before cooking or after attending public places, as studied in
304 Arena et al. (2014) could not be studied for norovirus sporadic cases.

305

306 Environmental factors could not be meta-analyzed properly because of irrelevant
307 subcategories or the insufficient number of studies and ORs. Untreated drinking water was
308 found significant, yet with only 2 ORs. This result is in agreement with described waterborne
309 outbreaks most often associated with multiple strains of norovirus (Matthews et al., 2012).
310 Surprisingly, attendance at a daycare center (but with only two publications in children)
311 remained not significant, even if frequently associated with outbreaks. Using public
312 transportation could not be studied. Furthermore, host-specific factors, such as
313 immunosuppressive treatment or other medical conditions, could not be studied due to data
314 scarcity. For the food category, it can be observed that the significant pooled OR for eating
315 uncooked, outside, or in a food market can be the consequence of poor food handling
316 practices by the caterer or even unwashed hands before having the meal. However this result
317 was only investigated in China and Vietnam. In this respect, outbreaks due to food handlers
318 are regularly investigated (De Wit et al., 2007; Hardstaff et al., 2018).

319

320 Seafood was found significant in the mixed population, yet there was not enough data to
321 distinguish shellfish from other seafood, and in particular raw oysters consumption from other
322 seafood. Oysters have been regularly contaminated and involved in outbreaks in France and
323 Europe (Le Guyader *et al.* 2010, Schaeffer *et al.* 2013, Lowther *et al.* 2012) but not fish or
324 crustaceans. Furthermore, other food products shown to be responsible for outbreaks (for
325 instance, soft fruits) were not included in the meta-analysis (Made *et al.* 2013, Le Guyader *et*
326 *al.* 2004), neither drinking untreated water nor recreational water (Boccia *et al.* 2002, Hoebe
327 *et al.* 2004).

328

329 The number of publications (14) concerning risk factors of sporadic norovirus infection or
330 norovirus gastroenteritis is low considering the disease burden in terms of morbidity. As an
331 example, the community incidence of norovirus associated with infectious intestinal disease
332 in the UK is estimated at around 4.5/100 person-years (Philipps *et al.*, 2010b). In comparison
333 with two other pathogens described in this meta-analysis issue, many more publications were
334 eligible for *Giardia* (72 studies) and for hepatitis A virus (78 studies), which increases the
335 power of the meta-analysis outcomes, and hence makes it easier to identify risk factors
336 associated to a given disease. This is the main limitation of the present meta-analysis. A
337 possible explanation is that outbreaks reports are numerous and used for source attribution
338 (Mead et al., 1999; Matthews *et al.* 2012, Bitler *et al.* 2013, Verhoef *et al.* 2015). However,

339 the extrapolation of results to sporadic cases is not so straightforward, because the population
340 associated with outbreaks can be different from the general population, can involve particular
341 strains or doses, and then the ranking of risk factors could be different. In The Netherlands,
342 the annual number of cases involved in outbreaks (all sources) was estimated around 30
343 /100,000, whenever the incidence of community-acquired (sporadic) norovirus cases (all
344 sources) was around 3,800/100,000 (Verhoef et al., 2013). Even if outbreaks of small size can
345 be under-detected, the relative part of outbreaks to the total burden of norovirus cases, base on
346 the study in The Netherlands can be estimated to be very low, below 1%.

347

348 In any case, the relative contribution of each source is not estimated most of the time in those
349 sporadic case-control studies, with some rare exceptions like the estimate of PAR (population
350 attributable risk fraction) in the publication of De Wit et al. (2003). Some studies
351 investigating risk factors of acute gastroenteritis without virus distinction (Arena et al., 2014)
352 were not included in this meta-analysis. A harmonized definition of the acute case, associated
353 with norovirus infection detection with proper control, checking for an existing immunity and
354 an absence of asymptomatic infection, would reduce the extra source of variability between
355 studies. However, for the last item, the risk of asymptomatic infection is limited: in a recent
356 meta-analysis, it was estimated that asymptomatic infection prevalence is around 7 % (Qi et
357 al., 2018).

358

359 The studies included did not distinguish between norovirus genogroups, but it may have an
360 impact on the intensity of transmission or the severity of the disease (Bull *et al.* 2010, Desai *et*
361 *al.* 2012). Due to the emergence of a new GII.4 variant in 2002, studying a period effect
362 would have been relevant. However, the small number of papers and the heterogeneous
363 distribution of publications/ORs before and after 2000 did not allow this analysis to be carried
364 out. Further analysis by genogroup, as it was investigated for outbreaks (Matthews et al.,
365 2012), distinguishing risk factor by genogroup, was not feasible in this meta-analysis, neither
366 geographical differences in risk factors.

367

368 Future case-control studies should investigate more precisely the different drinking water
369 treatment exposure, seafood categories, food-handled, and plant products (e.g., leafy greens,
370 soft fruits) as well as practices, such as food-handling, cooking or washing produce, in
371 relation with duration or frequency of exposure. Making an overall grid of risk factors and
372 transmission pathways by network analysis and prioritizing them based on biological

373 plausibility, outbreaks reported association, the management or recommendation possibilities
374 (Bosch et al., 2018; Guix et al., 2019) and percentage of potential exposure may be a good
375 start. Besides, such a study would make it possible to better characterize populations
376 considered sensitive (immunocompromised, children, the elderly) or places particularly at risk
377 (health facilities, public transit, schools/daycare centers, communities, contact with the
378 environment).. Finally, such studies could focus on person-to-person transmission, in relation
379 to hygiene factors and transfers of microorganisms.

380

381 **4. Conclusion**

382

383 This meta-analysis confirms the factors associated with the feco-oral pathway of transmission
384 and outbreaks studies (person-to-person, untreated water, seafood). However, due to the lack
385 of studies, precise factors cannot be studied, or are studied with a very low number of
386 publications (2 or 3 sometimes). This low number of eligible studies for studying sporadic
387 cases is not in relationship with the disease burden of norovirus.

388 It could be of interest to encourage specific investigation with norovirus sporadic
389 gastroenteritis (case/control, cohort or cross-sectional studies), in relation with the high
390 incidence of gastroenteritis associated with norovirus. So that in future, with a higher number
391 of included articles it would be feasible to explore risk factors in relationship with genogroup
392 or genotypes, type of populations, and geographical areas at regional scale.

393

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585 **Data statement**

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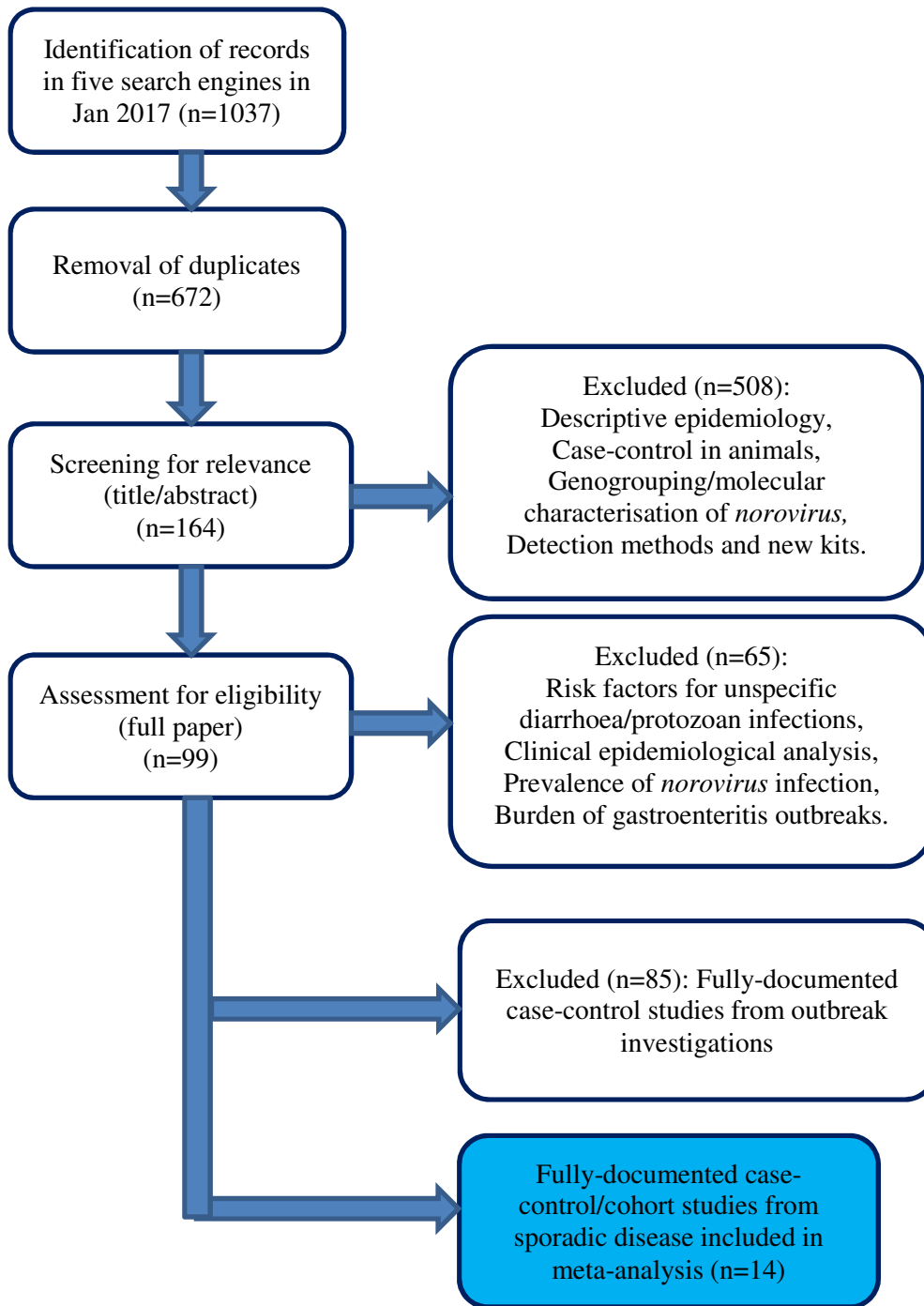


Figure 1: Flow chart of literature search for case-control and cohort studies of human norovirus infection

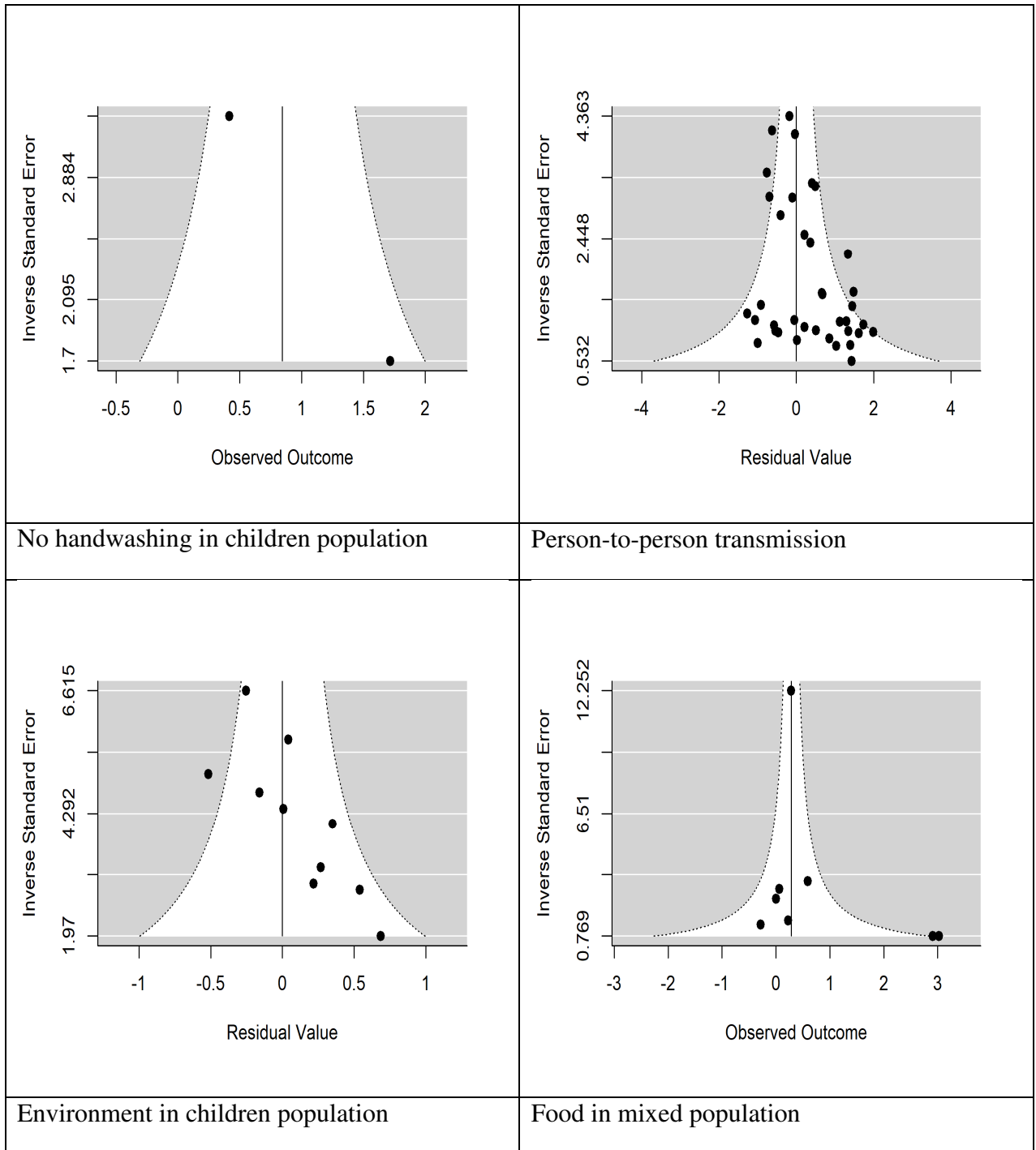
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Figure 2: Forest plot of OR and 95% interval for person-to person-transmission in children. Left-hand-side labels provide information on the reference, type of OR (raw or * adjusted) and the exposure as mentioned in the reference

Figure 3: Forest plot of OR and 95% interval for person-to person-transmission in the mixed population. Left-hand-side labels provide information on the reference, type of OR (raw or * adjusted) and the exposure as mentioned in the reference

Figure 4: Forest plot of OR and 95% interval for composite foods in children. Left-hand-side labels provide information on the reference, type of OR (raw or * adjusted) and the exposure as mentioned in the reference.

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668 Figure 5: Funnel plots of meta-analysis pooling odds-ratios of categorized risk factors: no
669 handwashing in children, person to person transmission, environment in children population,
670 and food in mixed population :

671 x-absciss observed outcome (or residuals of the model with moderators) with their corresponding
 672 inverse standard error in y-axis (Gonzales-Barron et al., 2019).

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676 **Tables**

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678 Table 1: Characteristics of primary studies investigating risk factors for acquiring sporadic
 679 norovirus infection included in the meta-analysis

Study ID	Country	Study period	Population	Design	Analysis & model**	# cases /controls	Potential for bias in meta-analysis*** Final ORs /removed*
Dai et al. 2010	China	Oct 2003 - Jan 2006	Children	Matched	Uni-UL Multi-UL	112 cases 357 controls	No 8
Enserink et al. 2015	Netherlands	2010 - 2012	Children	Unmatched	Multi-UL	504 cases 4693 controls	Yes 3
Fretz et al. 2005	Switzerland	2001 - 2003	Mixed	Matched	Uni- CL	73 cases 73 controls	No 5
Grant et al. 2012	USA	Mar 2002 - Oct 2003	Children	Unmatched	Multi-UL	62 cases 50 controls	No 1
Henke-Gendo et al. 2009	Germany	Jan 2005 - Jun 2008	Mixed	Unmatched	Uni-Chi Multi-UL	20 cases 58 controls	Yes 6
Heusinkveld et al. 2016	Netherlands	Apr 2013 - Oct 2014	Children & adult	Unmatched	Multi-UL	60 cases 1843 controls	No 6
Karsten et al. 2009	Germany	Jan - Dec 2004	Mixed	Unmatched	Multi-UL	186 cases 1399 controls	No 2
My et al. 2013	Vietnam	May 2009 - Dec 2010	Children	Unmatched	Uni-Chi Multi-UL	242 cases 592 controls	No 13
Peasey et al. 2004	Mexico	Nov 1993 - Jan 1995	Children	Unmatched	Uni-Chi Uni-UL	83 cases 174 controls	No 9
Phillips et al.(a) 2010	UK	1993 - 1996	Children Mixed	Matched	Multi-UL	81 cases 461 controls 156 cases 1206 controls	No 19
Relic et al. 2015	Serbia	2010 - 2011	Mixed	Unmatched	Uni-Chi	36 cases 51controls	No 1
Tang et.al 2013	Taiwan	Aug 2011 - Jul 2012	Mixed	Unmatched	Uni-Chi	17 cases 138 controls	No 2
De Wit et al. 2003	Netherlands	1999	Mixed Children	Matched	Uni-Chi Multi-CL Uni-Chi Multi-CL	152 cases 152 controls 105 cases 105 controls	No 26
Xue et al. 2015	China	May 2012 - Aug 2013	Mixed	Unmatched	Uni-Chi	903 cases 3038 controls	No 1

680 (*) Number of ORs not included in the meta-analysis for presenting mean values lower than 0.5.

681 (**) Uni-Chi: univariate Analysis with Chi-square; Uni-UL: univariate analysis with Unconditional Logistic
682 regression; Multi-CL: multivariate analysis with conditional logistic regression; Multi-UL: multivariate analysis
683 with unconditional logistic regression
684 (***)Primary studies that passed the screening for relevance were marked as having potential for bias (“Yes”)if
685 they failed to meet at least one of the methodological quality assessment criteria: details in “systematic review”
686 and “descriptive statistics section”.
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 690 Table 2: Characteristics of primary studies investigating risk factors for acquiring sporadic
 691 norovirus infection included in the meta-analysis in term of definition of cases/control and
 692 recruitment of cases

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Study ID	Definition infection or case & infection /control	Recruitment of cases
Dai et al. 2010	AcGE+positive RT-PCR / AcGE negative RT-PCR+Rotavirus PCR positive	Hospital
Enserink et al. 2015	Nov Positive with real time multiplex PCR assays/Nov negative	Day Care Centers
Fretz et al. 2005	AcGE+positive RT-PCR+negative other pathogens/ no AcGE	General practitioner based
Grant et al. 2012	AcGE +norovirus rRT-PCR positive/negative	Placebo group of oral PRV Rota Teq vaccine; children below 9 months old
Henke-Gendo et al. 2009	rRT-PCR positive after 10 days/ rRT-PCR positive not after 10 days	Hospitals
Heusinkveld et al. 2016	Multiplex RT-PCR positive/ RT-PCR negative	Preschool children from population registries
Karsten et al. 2009	Positive with nested RT-PCR & AcGE/negative with nested RT-PCR	physicians
My et al. 2013	RT-PCR positive& AcGE /negative and no AcGE	Hospitals
Peasey et al. 2004	Elisa positive/Elisa negative	Random samples of household
Phillips et al. 2010a	AcGE with rRT-PCR positive for GII and RT-PCR for GI+electron microscopy / norovirus negative control+without GE symptoms	Cohort in community & general practitioner
Relic et al. 2015	AcGE+positive with immunochromatography assay/ control =AcGE+ negative immunochromatography	Microbiology laboratory of Public health
Tang et.al 2013	AcGE+RT-PCR positive/ RT-PCR negative noAcGE+RT-PCR positive/ noAcGE+RT-PCR negative	Hospital
De Wit et al. 2003	RT-PCR positive+AcGE/ no AcGE	Community cohort
Xue et al. 2015	AcGE +Positive with rRT-PCR/ AcGE + negative rRT-PCR	Hospitals

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 695 Legend: AcGE: acute gastroenteritis, RT-PCR: Reverse Transcription Polymerase Chain Reaction; rRT-PCR Real Time
 696 Reverse Transcription Polymerase Chain Reaction

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700 Table 3: Significant results of the meta-analysis on main risk factors for norovirus infection

Population	Risk factor	Pooled OR [IC95%]	N/n *	p-value of risk factor	Publication bias p-value	Points removed **	Heterogeneity analysis***
Lack of hygiene							
Children	No handwashing	2.329 [1.049 - 5.169]	2/2	0.0377	0.050	0	$\tau^2=0.154$ Q(df = 1) = 3.846; p-val = 0.050 $s^2=0.844$ $I^2=15.455$
Person to person by population							
Mixed		3.002 [2.502 - 3.602]	3/21	<.0001	0.014	0	$\tau^2=0.774$ QE(df = 36) = 167.35; p-val < .0001 $s^2=0.876$ $I^2= 46.912$
Children		4.648 [2.092- 10.325]	5/17	0.0002			
Environment							
Mixed	Untreated drinking water (excluding tap water)	2.680 [1.081 - 6.643]	2/2	0.0333	0.138	0	$\tau^2=0.029$ $s^2=0.890$ $I^2= 3.198$
Children	Farm	1.563 [1.082 - 2.257]	3/3	0.0172	0.013	0	$\tau^2=0.013$ QE(df = 7) = 12.960; p-val = 0.073 $s^2= 0.136$ $I^2=8.969$
Food							
Mixed	Seafood	2.270 [1.299 - 3.968]	2/3	0.0040	0.013	0	$\tau^2=0$ QE(df = 4) = 6.4028; p-val = 0.171 $s^2=1.187$ $I^2=0$
Children	Composite food	4.541 [3.461 - 5.958]	2/5	<.0001	0.108	0	$\tau^2=0$ QE(df = 9) = 5.4659 ; p-val = 0.7920 $s^2=0.131$; $I^2=0$

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*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).

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713 Table 4: Non-significant risk factors (coming from non-isolated studies)

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Population	Risk factor	Pooled OR [IC95%]	N/n*
Animals			
All	Contact with animals	1.199 [0.557 - 2.577]	5/7
Environment			
Mixed	Drinking water	1.753 [0.969 - 3.171]	3/4
Children	Daycare	1.342 [0.946 - 1.902]	2/3
All	Daycare	1.391 [0.857 - 2.257]	3/4

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716 *N/n Number of studies/number of OR

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