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

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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-

6.643]) and farm environment (children population). Indirect transmission also involved the food pathway, which was finally found significant with consumption of seafood (mixed population) (pooled OR=2.270; 95% CI: [1.299-3.968]) and composite food (eating outside/uncooked mixed and young population) (pooled OR=4.541; 95% CI: [3.461-5.958]). These results are coherent with the findings from studies on outbreaks. . However, a too broad definition of exposure factors limited the interpretation of results, as occurred with the seafood pathways that combined fish and shellfish. Other factors such as consumption of Food-handled products or the type of drinking water deserve to be better investigated. Furthermore, better harmonization in case definition and appropriate case-control or cross-sectional studies would allow better addressing sporadic cases risk factors, especially for susceptible populations, such as children, elderly or immunosuppressed persons.

1. **Introduction**

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

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

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

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

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

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

2. Material and methods

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

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

2.1 Systematic review

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

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

2.2 Data synthesis

The joint meta-analytical data was first described using basic statistics. Next, data was partitioned into subsets of categories of risk factors: travel, host-specific factors and transmission pathways related to person-to-person contagion, animal contact, environmental exposures and food vehicles. The variable population was stratified into mixed (adults or undefined) and children (at least under 16 years old). Meta-analysis models were then fitted to each of the data subsets in order to estimate the overall ORs associated to the risk factors. The meta-analytical models were fitted separately by population type. The statistical analysis was designed to assess the effect of the geographical region. 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. A Geographical region (Asia, North America, South America, Africa, Europe, Oceania) was removed from a particular meta-analysis partition only if its pooled ORs were different from those associated with the other regions or if less than 3 ORs represented the region (Gonzales-Barron et al., 2019. The situation of exclusion of a particular region never occurs for norovirus, because no strong heterogeneity beween regions was detected (when this analysis was feasible).

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

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

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

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

Results

3.1 Descriptive statistics

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

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

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

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

3.2 **Meta-analysis results**

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

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

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

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

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

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

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

For all the meta-analytical models reported in Table 3, the statistical tests indicated the presence of potential significant publication bias below 5%, with exception of no handwashing, person-to-person transmission, and environment and food in children. For better assessing the publication bias, the funnel plots for models with significant publication bias are given in Figure 5 "No handwashing" has too few ORs to be taken into consideration. For "person-to-person" and "environment" in children population, there was an asymmetry towards lack of small studies with smaller ORs. Furthermore, since there were very few ORs for food products in the mixed population, an overall trend in the funnel plot is not obvious, and is probably linked to the heterogeneity in the different kind of food products in this category. Moreover, the intra-class correlation, as percentage of the total variance that is explained by the variation between studies, "I^2", was always below high heterogeneity (<75%) (Table 1). Most often, remaining between-study heterogeneity (significant p-val below 0.05 for Q or QE) was not observed for the data partitions, except for person-to-person transmission.

3. Discussion

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

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

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

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

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

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

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

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

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

4. Conclusion

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

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

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Data statement

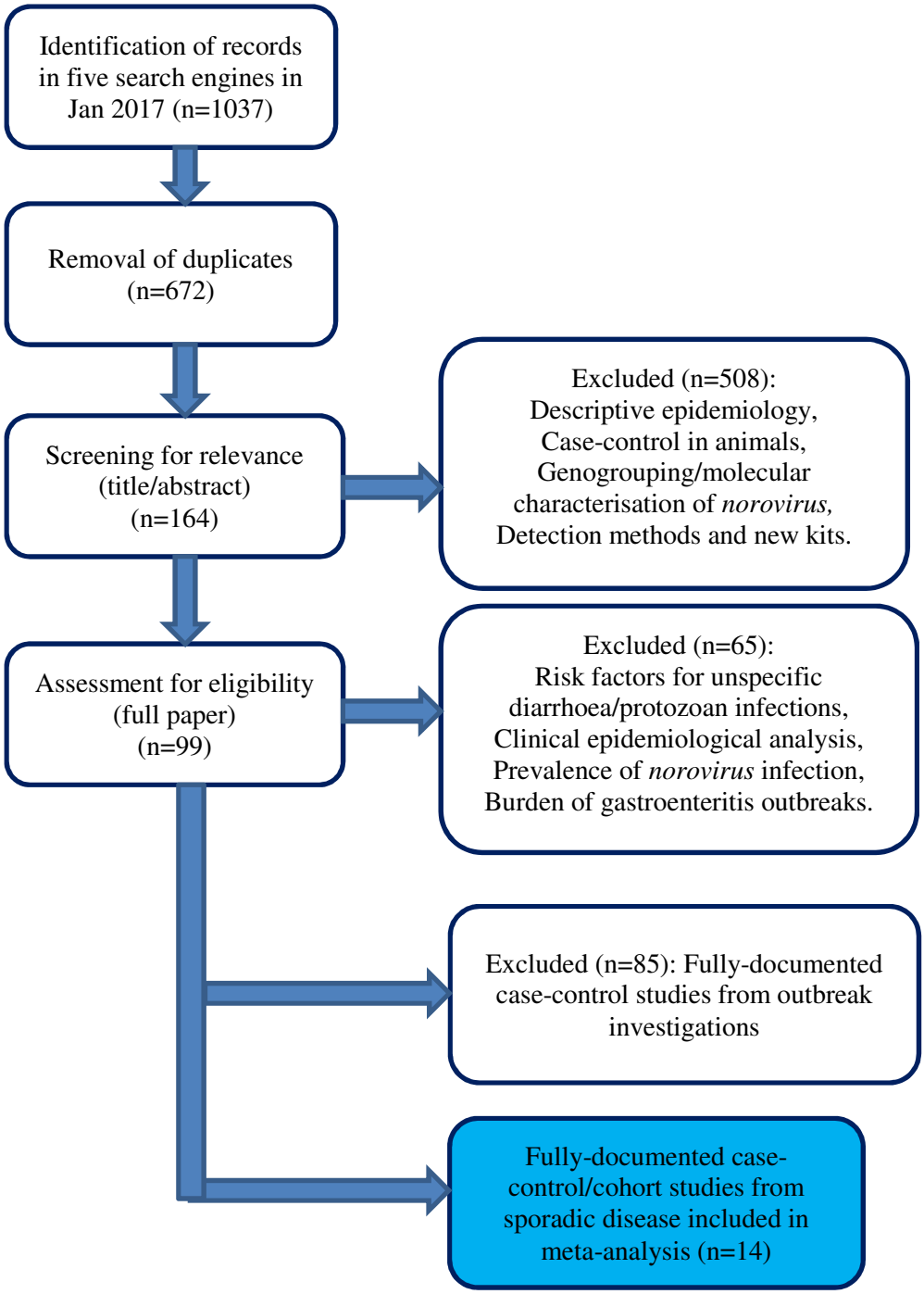
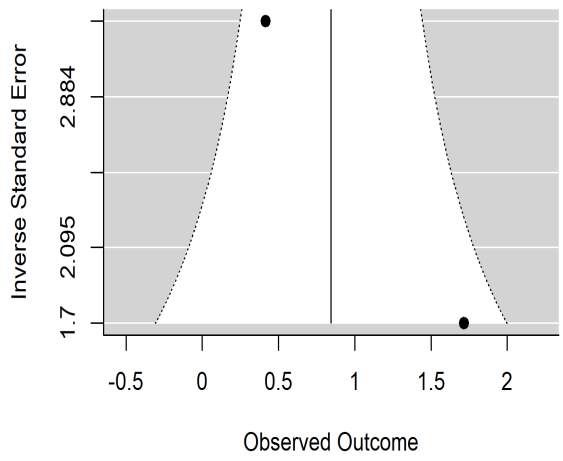


Figure 1: Flow chart of literature search for case-control and cohort studies of human norovirus infection

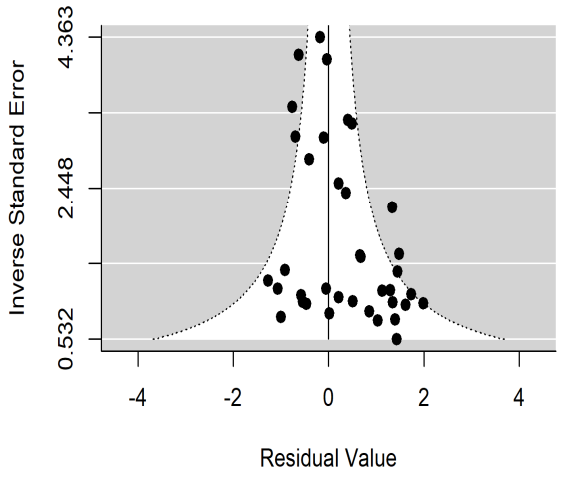
Figure 2: Forest plot of OR and 95% interval for person-to person-transmission in children. Left-hand-side labels provide information on the reference, type of OR (raw or * adjusted) and the exposure as mentioned in the reference

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

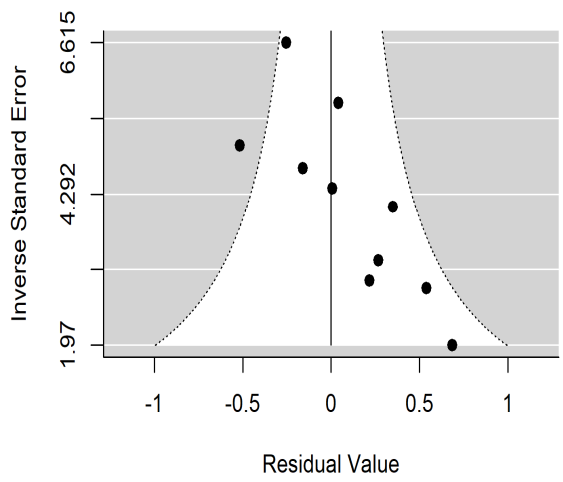
Figure 4: Forest plot of OR and 95% interval for composite foods in children. Left-hand-side labels provide information on the reference, type of OR (raw or * adjusted) and the exposure as mentioned in the reference.



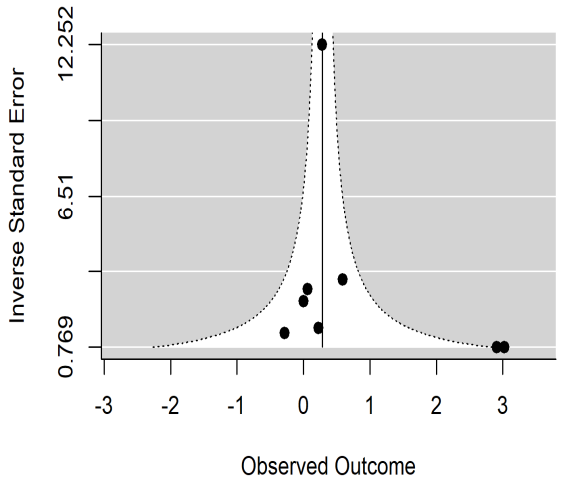
No handwashing in children population



Person-to-person transmission



Environment in children population



Food in mixed population

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

671 x-abciss 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**
677
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.

(**) Uni-Chi: univariate Analysis with Chi-square; Uni-UL: univariate analysis with Unconditional Logistic regression; Multi-CL: multivariate analysis with conditional logistic regression; Multi-UL: multivariate analysis with unconditional logistic regression

(***)Primary studies that passed the screening for relevance were marked as having potential for bias ("Yes")if they failed to meet at least one of the methodological quality assessment criteria: details in "systematic review" and "descriptive statistics section".

Table 2: Characteristics of primary studies investigating risk factors for acquiring sporadic norovirus infection included in the meta-analysis in term of definition of cases/control and recruitment of cases

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

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

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	τ^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	τ^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	τ^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	τ^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	τ^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	τ^2=0 QE(df = 9) = 5.4659 ; p-val = 0.7920 s^2=0.131 ; I^2=0

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

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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

715

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

717