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Risk factors for sporadic *Yersinia enterocolitica* infections: a systematic review and meta-analysis

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ABSTRACT

Yersinia enterocolotica is an important causative agent of diarrheal illness. A systematic review and meta-analysis of case-control studies were performed to determine the main risk factors associated with sporadic *Y. enterocolitica* infections. Suitable scientific articles published between 1987 and 2017 were identified through a systematic literature search and subject to methodological quality assessment. From each study, odds ratios (OR) were extracted or calculated, as well as study characteristics such as population type, design, type of model used and risk factor categorization. Mixed-effects meta-analytical models were adjusted by population type to appropriate data partitions. From 807 identified references, the quality assessment stage was passed by 14 case-control studies focusing on sporadic *Y. enterocolitica* infections which provided 165 ORs for meta-analysis. All studies considered *Y. enterocolitica* as the cause of sporadic infections and are mainly located in Europe.

The meta-analysis identified host-specifics factors, animal and food exposures as significant risk factors. The meta-analysis confirms the predominant role of the pig reservoir. The occupational contact with pigs and the consumption of pork meat are significantly associated with sporadic *Y. enterocolitica* infections occurrence. The consumption of raw or undercooked pork meat is also a very important risk factor. Untreated drinking water was also identified as risk factor. Further studies with other enteropathogenic *Yersinia* species, especially *Y. pseudotuberculosis*, and/or from other continents would help to refine conclusions of the meta-analysis of the risk factors of yersiniosis.

1. Introduction

The genus *Yersinia* is composed of 19 species, among which two are enteropathogenic to humans (*Y. enterocolitica, and Y. pseudotuberculosis*) (Savin et al., 2019). Enteropathogenic *Yersinia*are mainly found in temperate or cold regions, such as Central and Northern Europe, New-Zealand and North America. Strains of *Yersinia* are ubiquitous and occur in soil, surface water, food and in the digestive tract of various animal species (Le Guern et al., 2016).

Y. enterocolitica is the main species in the genus associated with yersiniosis, which can be defined as a mild-moderate self-limiting gastroenteritis (Galindo et al., 2011). *Y. enterocolitica* is subdivided into 6 biotypes (1A/1B, 2, 3, 4, 5) based on biochemical tests and more than 70 serotypes (Le Guern et al., 2016; Wauters, 1987). *Y. enterocolitica* infection is usually characterized by diarrhea, fever and abdominal pain (Savin et al., 2008). Patients do not always present all three symptoms. Complications such as reactive arthritis or, more rarely, sepsis can also be observed in individuals (Hoffmann and Scallan Walter, 2019; Rosner et al., 2013). Symptoms develop 4 to 7 days after exposure and persist for 5 to 14 days, or several weeks in the case of diarrhea (Laukkanen-Ninios et al., 2012).

Y. enterocolitica infections are the fourth most frequently reported bacteriologically related foodborne zoonosis in Europe (EFSA and ECDC, 2019). Reported incidence varies according to country, the method used for diagnostic and the performance of the reporting system. It ranges from less than 1 case per 100,000 in the US (Tack et al., 2019)

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up to 19.2 in New Zealand (Strydom et al., 2019). Yet the number of illness could be higher when considering underreporting and underdiagnosis (Van Cauteren et al., 2017). As an example, in France, the corrected annual community incidence rate was estimated at 36 cases per 100,000 for yersiniosis, about 30 times higher than the reported incidence rate (Van Cauteren et al., 2017). Microbiological and epidemiological investigations make it possible to identify outbreaks and to trace back the food at the origin of the human cases (Espenhain et al., 2019). Although outbreaks are identified (Konishi et al., 2016; MacDonald et al., 2012), a majority of yersiniosis cases caused by *Y. enterocolitica* are not associated with any known outbreak (Marimon et al., 2017) and are classified as sporadic cases. The question of specific environmental or food exposures and their respective weight for these sporadic cases arise.

A large variety of methodological approaches for source attribution of sporadic cases is available (Mughini-Gras et al., 2019). Yet, very few source attribution studies have been carried out for yersinosis. Expert elicitation was the main method applied so far (Batz et al., 2012; Zanabria et al., 2019).

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

The aim of this study is to perform a systematic review of case-control studies for human sporadic*Y. enterocolitica* infections, and, subsequently, to perform a meta-analysis to synthesize data on factors associated with sporadic infection, combining the odds ratio from a selection of relevant studies (Gonzales-Barron et al., 2019).

2. Methods

The systematic review process as well as the meta-analysis model are described in depth in a methodological paper (Gonzales-Barron et al., 2019).

2.1. Systematic review

The keywords were defined attending the review question which is to evaluate the association between a (risk) factor and sporadic *Y. enterocolitica* infections risk in a population exposed to it. This review question was identified to have a typical PECO structure (Population, Exposure, Comparator and Outcome as key elements) (EFSA, 2010)..The literature search was conducted in March 2017 using a combination of keywords related to (1) "*Yersinia enterocolitica* OR yersiniosis", (2) "case-control OR risk factor OR cohort" (3) "infection OR disease", joined by the logical connector AND. Systematic searches using a combination of suitable keywords were conducted using five bibliographic search engines (ISI Web of Science, PubMed, Scielo, Science Direct and Scopus). The literature search was conducted for English, French, Portuguese and Spanish languages.

The screening criteria followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method (Moher et al.,

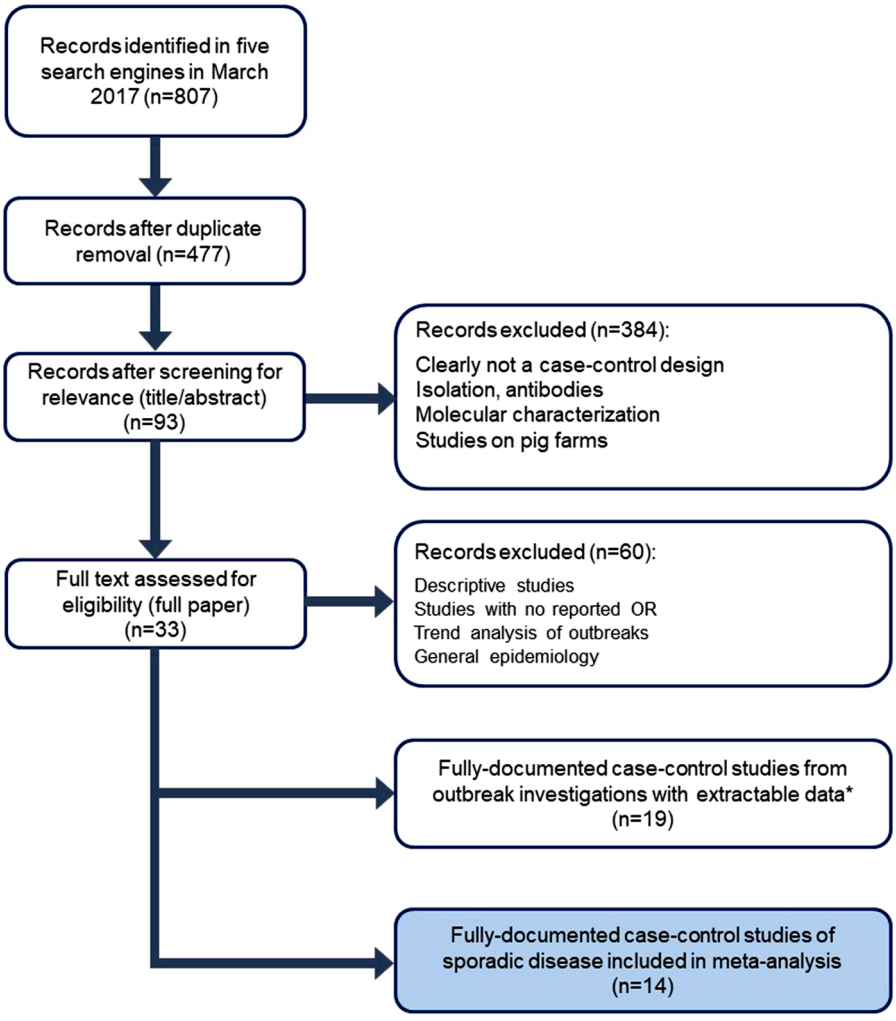

Fig. 1. Flow chart of the literature search for case-control studies of sporadic *Y. enterocolitica* infections. (*) Kept in JabRef file and available upon request.

Table 1
Characteristics of case-control/cohort studies investigating sources of sporadic *Y. enterocolitica* infections included in the meta-analysis.

Study ID	Country	Study period	Population	Study & Design	Analysis & Model* (number of ORs)	# cases/controls	Quality
Boqvist et al. 2009	Sweden	2004	Children <6 y/o	Matched	Uni-UL (12) Multi-UL (5)	117 cases 339 controls	Good
Cherchi et al. 1995	Italy	1993-1994	Mixed	Prospective cohort, UM	Uni-Chi (1)	16 cases 228 controls	Good
Hansen et al. 2006	Denmark	2006	Mixed	Unmatched	Uni-Chi (2)	129 cases 165 controls	Good
Huovinen et al. 2010	Finland	2006	Mixed	Matched	Uni-CL (38)	54 3-4/O:3 or 2/O:9 133 controls 98 Biotype 1A 251 controls	Good
Ostroff et al. 1992	Norway	1988-1990	Mixed	Matched	Uni-MH (1)	66 O:3 131 controls	Good
Ostroff et al. 1994	Norway	1988-1990	Mixed	Matched	Uni-CL (11)	67 O:3 132 controls	Good
El Qouqa et al. 2011	Palestine	2010	Children <12 y/o	Matched	Uni-Chi (8) Multi-UL (3)	16 cases 128 controls 16 cases 144 GI controls	Good Poor
Rosner et al. 2012	Germany	2009-2010	Children Mixed	Unmatched	Uni-UL (12) Multi-UL (11)	571 cases 1798 controls	Good
Sæbø et al., 1994	Norway	1988-1990	Adult	Unmatched	Uni-Chi (15) Multi-UL (1)	56 seropositive (IgG+) (O:3) 699 seronegative IgG-	Good
Satterthwaite et al. 1999	New Zealand	1988-1993	Mixed	Unmatched	Uni-UL (18)	186 cases 360 controls	Poor
Seuri & Granfors 1992	Finland	1991	Mixed	Cohort Unmatched	Uni-Chi (16)	29 O:3/O:9 233 controls	Good
Skjerve & Kapperud 1991	Norway	1991	Mixed	Matched	Uni-MH (2)	63 cases 123 controls	Good
Tauxe et al., 1987	Belgium	1987	Mixed	Unmatched	Uni-Chi (1)	40 cases ? controls**	Good
Wilson et al. 2008	New Zealand	2006	Mixed	Unmatched	Uni-Chi (7)	285 Yersinia 5038 Campylobacter	Poor

(*) Analysis can be univariate (Uni) and multivariate (Multi) while model can be chi-square (Chi), Mantel-Haenzel (MH), unconditional logistic (UL) and conditional logistic (CL)
(**) Number of controls not stated in the study

2009). Each reference record was screened by at least two persons for relevance for inclusion in the meta-analysis study, and subsequently, the methodological quality of the "candidate" studies was assessed using preset quality criteria. The first criterion for inclusion was related to the definition of the disease. The included studies should have used a laboratory-based definition of a case, based on a detection or isolation from cultures of the cases. The second criterion refers to the study design. Only the case-control study design was considered.

Moreover, the methodological quality of each "relevant" primary case-control study was assessed using a checklist comprised of six areas of concern. It concerns the appropriate selection of the controls in order to avoid selection bias; the adjustment to correct for confounders, the criteria for the comparability between cases and controls; the data analysis appropriate to the type of design, matched or unmatched; the responses rates for the exposed and control groups; and the provision of crude data and/or adjusted ORs and either confidence interval or p-value. All these points permitted to assess the overall quality of underlying methods, appropriate statistics, sensible data and quality of reporting/interpretation.

Finally, the quality and completeness of statistical analysis were assessed. Primary studies that passed the screening for relevance were marked as having the potential for bias if they failed to meet at least one of the methodological quality assessment criteria. After careful data extraction, meta-analysis models were adjusted within appropriate risk factor data partitions in order to estimate overall ORs, extracting variability due to primary studies and type of statistical analysis. Diagnostics based on Cook's distance was assessed for every meta-analysis model in order to remove any influential OR originated from studies deemed as having some potential for bias.

2.2. Data synthesis

The joint meta-analytical data was first described using basic descriptive statistics. The number of ORs per country, per year, and per type were calculated. Next, data was partitioned into subsets of categories of risk factors. The used source categorization scheme included travel, host-specific factors and hierarchical pathways of exposure – comprising person-to-person, animal, environment and food routes of transmission. Gonzales-Barron et al. (2019) provides the full list of risk factors, categories and subcategories. Food class and handling are also used for exploring in depth food related factors. The full hierarchy of risk factors is provided in Appendix 1.

Meta-analysis models were then fitted to each of the data partitions or subsets in order to estimate the overall OR due not only for food vehicles but also to travel, host-specific factors and transmission pathways related to person-to-person transmission, animal contact and environmental exposures. In accordance with Gonzales-Barron et al. (2019), the meta-analytical models were fitted separately by population type, which are children and mixed population. For some food classes, the effects of handling (i.e., eating raw, undercooked) and setting (i.e., eating out) were assessed by dividing the mean ORs when food was mishandled (or, alternatively, when food was prepared outside the home) by the base ORs.

The statistical analysis was designed to assess the effect of study period and analysis type (univariate/multivariate) on the final result. All meta-analytical models were essentially weighted random-effects linear regression models. A random effect term allow taking into account the study effect ("dependence between studies") nested into the risk factors categories (Gonzales-Barron et al., 2019). Once a meta-analytical 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 and statistical tests. Heterogeneity between studies was assessed by three indicators, 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 conducted in the R software implemented with the *metafor* package (Viechtbauer, 2010).

Results

Table 2.
Results of the meta-analysis on the main risk factors of sporadic *Y. enterocolitica* infections.

Population	Risk factor	Pooled OR [IC95%]	N/ n*	p-value of risk factor	Publication bias p-value	Points removed **	Heterogeneity analysis***
Host specific							
Mixed	Host specific	3.132 [1.191 - 8.235]	4/5	0.021	0.956	0	Tau2=0.777 Q(df = 4) = 35.551, p-val < .0001 S2=1.241 I2=38,491
Animal							
Mixed	Occupational exposure	1.434 [1.164 - 1.766]	2/ 17	0.001	0.155	1	Tau2=0,090 QE(df = 28) = 32.017, p-val = 0.274 S2=0.220 I2=28.915
Environment							
Mixed and Children	Untreated drinking water	1.804 [1.230 - 2.645]	5/ 10	0.003	0.221	1	Tau2=0.295 QE(df = 16) = 25.349, p-val = 0.064 S2=0.232 I2=55.919
Children	Playground	1.580 [1.343 - 1.857]	2/5	<.0001			
Food							
Mixed	Meat	1.870 [1.093 - 3.200]	6/ 42	0.0224	0.008	2	Tau2=0.372 QE(df = 59) = 368.714, p-val < .0001 S2=0.538 I2=40.903
Children	Meat	3.119 [1.550 - 6.274]	2/ 15	0.001	0.013	0	Tau2=0.230 Q(df = 14) = 38.705, p-val = 0.0004 S2=0.620 I2=27.056

*N/n Number of studies/number of OR;** points removed by sensitivity analysis, all results are given after removing data concerned; ***Between-study variability (τau2), test for residual heterogeneity (QE), variance of residuals (s^2), intra-class correlation (I^2)

Table 3
Results of the meta-analysis on disaggregated food risk factors of sporadic *Y. enterocolitica* infections.

Food category	Food sub-category	Population	Pooled OR [IC95%]	N/ n*	p-value of risk factor	Publication bias p-value	Points removed	Heterogeneity analysis***
Meat	Pork	Mixed	1.995 [1.793 - 2.219]	4/ 13	<.0001	0.093	3	Tau2=0.000 QE(df = 33) = 142.376, p-val < .0001 S2=0.403 I2=0.000
Meat	Pork	Children	3.416 [1.893 - 6.165]	2/8	<.0001	0.020	0	Tau2=0.145 QE(df = 13) = 27.899, p-val = 0.009 S2=0.539 I2=21.127
Meat	Pork	Mixed + Children	2.638 [1.584 - 4.395]	5/ 21	0.0002	1.053e-07	1	Tau2=0.225 Q(df = 20) = 129.349, p-val < .0001 S2=0.731 I2=23.543
Composite	Fast food	Mixed	1.198 [1.097- 1.308]	3/4	<.0001	3.633e-07	0	Tau2=0.152 QE(df = 8) = 40.115, p-val < .0001 S2=0.546 I2=21.756
RTE food		Mixed + Children	1.096 [1.010 - 1.190]	4/7	0.028	0.139	1	Tau2=0.000 Q(df = 6) = 8.147, p-val = 0.228 S2=0.202 I2=0.000

*N/n Number of studies/number of OR;** points removed by sensitivity analysis, all results are given after removing data concerned; ***Between-study variability (τau2), test for residual heterogeneity (QE), variance of residuals (s^2), intra-class correlation (I^2).

2.3. Descriptive statistics of the case-control studies

In the systematic review of risk factors pertaining to sporadic*Y. enterocolitica* infections, a total of 807 bibliographic sources were identified using the defined keywords in the five search engines, from which only 33 passed the full assessment for eligibility comprising case-control/case and cohort studies from both sporadic illnesses and outbreaks (Fig. 1). A total of 19 fully-documented case-control studies investigated the source(s) of outbreaks and were thus not included in the study. The meta-analysis was undertaken using 14 primary studies focused on sporadic disease (Fig. 1). These published studies were conducted between 1987 and 2010. Table 1 compiles a list of the case-control studies along with their main features.

The eligible studies jointly provided 165 categorized odds-ratios for meta-analysis. A total of 66 ORs were retrieved from 8 case-control studies performed before the year 2000, while 99 ORs were excerpted from 6 case-control studies undertaken after 2000. The majority of primary studies investigated sporadic*Y. enterocolitica* infections caused by undetermined serogroups (9 case-control studies) representing 72% of the ORs. The countries whose case-control studies contributed the largest body of results for sporadic *Y. enterocolitica* infections were Finland (2 studies, 55 ORs), Norway (4 studies, 30 ORs), New Zealand (2 studies, 25 ORs) and Germany (1 study, 23 ORs).

Twelve case-control studies investigated pathways of exposure in

Table 4
Effect of food handling on pooled odd ratios for sporadic *Y. enterocolitica* infections.

Risk Factor	Risk factor precise	Pooled OR [IC95%]	N/ n*	p-value of risk factor	OR ratios and CI95%	Publication bias p-value	Points removed	Heterogeneity analysis***
Pork and other meats (1)	Raw	5.412 [2.180 - 13.436]	3/5	<.0001	4.374 [2.203 - 8.683]	0.001	0	Tau2=0.196 QE(df = 25) = 44.6561, p-val = 0.0091 S2=0.329 I2=37.367
	Undercooked	4.354 [2.650 - 7.153]	3/9	<.0001	3.519 [2.678 - 4.622]			
	Base	1.237 [0.990 - 1.547]	6/ 14	0.062	/			
Pork and other meats (2)	Undercooked+ raw	4.215 [2.657 - 6.684]	5/ 14	<.0001	3.417 [2.681 - 4.355]	0.001	0	Tau2=0.037QE(df = 26) = 44.765, p-val = 0.013 S2=0.330 I2=10.022
	Base	1.233 [0.991 - 1.534]	6/ 14	0.060	/			

*N/n Number of studies/number of OR;** points removed by sensitivity analysis, all results are given after removing data concerned; ***Between-study variability (τau2), test for residual heterogeneity (QE), variance of residuals (s^2), intra-class correlation (I^2).

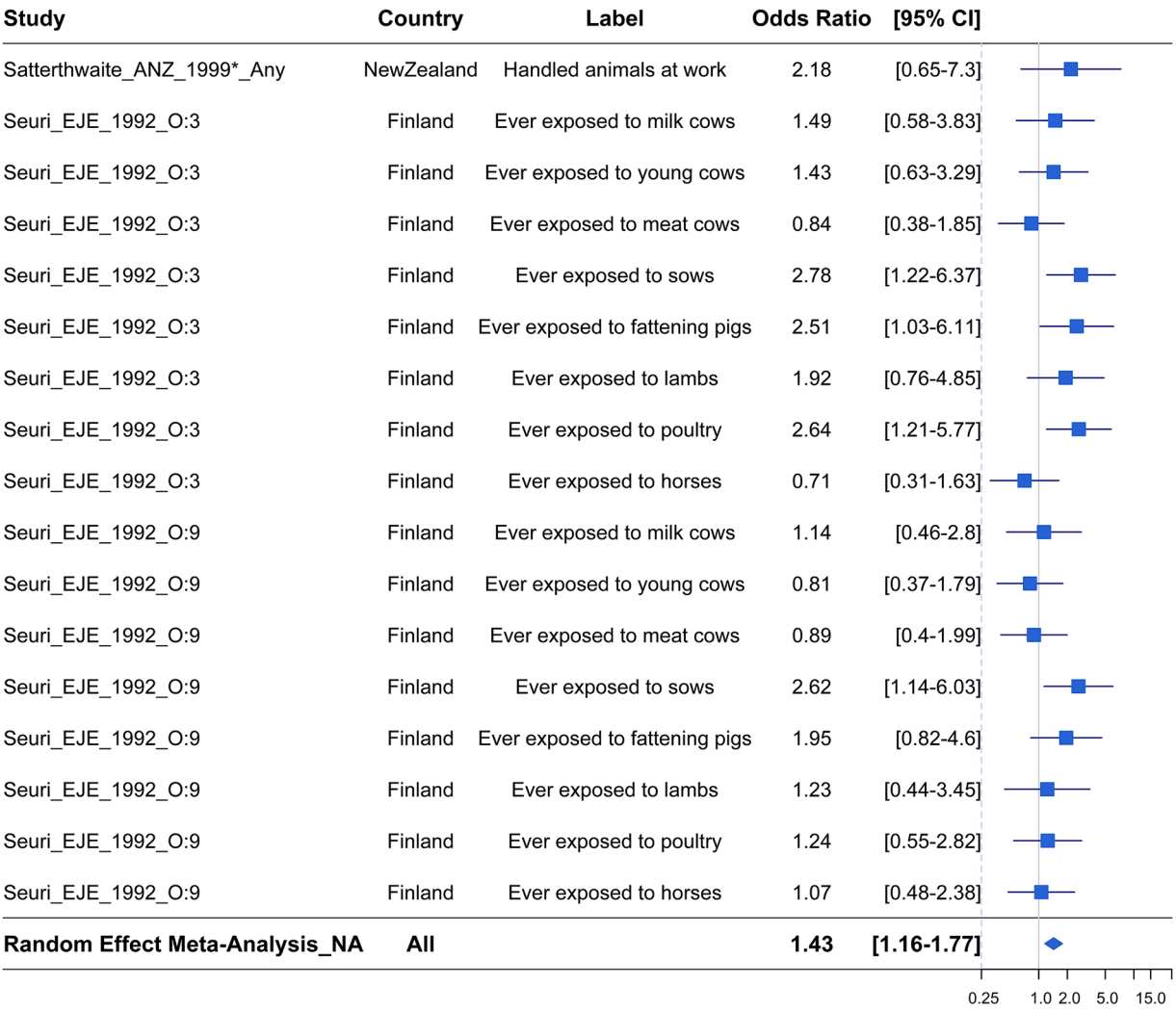

Fig. 2.. Forest plot of the associations of yersiniosis with the category of "occupational animal contact" in the mixed population (*adjusted OR, N=17 ORs).

adult or mixed population, while only three case-control studies had children as the target population. The only primary study investigating determinants of disease in both children and mixed population was that of Rosner et al. (2012) (Table 1). Whereas 80% of the ORs originated from exposures evaluated in the mixed/adult population, 20% of the ORs were quantified from ill children cases. As a rule, because of their distinct routes of exposure, the ORs for children and mixed populations were not joined in a single meta-analysis model, but in separate meta-analyses. Data from both populations were merged only when the ORs belonging to the children population were too few to run a separate meta-analysis model.

2.4. Meta-analysis

For every data partition, the meta-analyzed risk factors are presented in summary tables only when significant (Tables 2, 3 and 4) and when more than one study inform the risk factor. Pooled ORs were considered significant when the lower bound of the 95% CI was equal or greater than 1. Appendix-2 provides values for non-significant factors as well as significant risk factors that arise from a single study.

2.5. Risk factors associated with non food-related transmission pathways

Among travel, host-related factors, contact with the environment and animals, only a few categories were found as significantly associated with sporadic *Y. enterocolitica* infection cases (Table 2).

Among the main risk categories that were amenable to be meta-analysed, the host-specific factors, associated with chronic diseases in the mixed population, represented as a whole the most important risk factor for acquiring yersiniosis (overall OR=3.132; 95% CI: 1.191 – 8.235). Malnutrition was also associated to yersiniosis in the children population but it arises from a single study (Appendix 2).

Within "contact with animals" categories, the occupational animal contact (overall OR=1.434; 95% CI: 1.164 – 1.766) was the only significant risk factor of sporadic *Y. enterocolitica* infections. It is worthy to mention that, within the mixed population, the significance is mainly explained for occupational exposure data by exposure to pigs (Fig. 2). Contacts with pets or occasional contact with farm animals were not associated with sporadic *Y. enterocolitica* infections. A single study explore the contact with wild animals (Rosner et al., 2012) and it does not allow us to draw any conclusions for this risk factor.

For the mixed population and children, sporadic *Y. enterocolitica* infections occurred more frequently among people exposed to untreated drinking water (overall OR=1.804; 95% CI: 1.230 – 2.645) (Fig. 3). For children, activities in playground were associated with sporadic *Y. enterocolitica* infections (OR=1.580; 95% CI: 1.343 – 1.857).

In all the meta-analytical data partitions, there was no effect of the study period (before and after 2000) on the measured ORs. The meta-

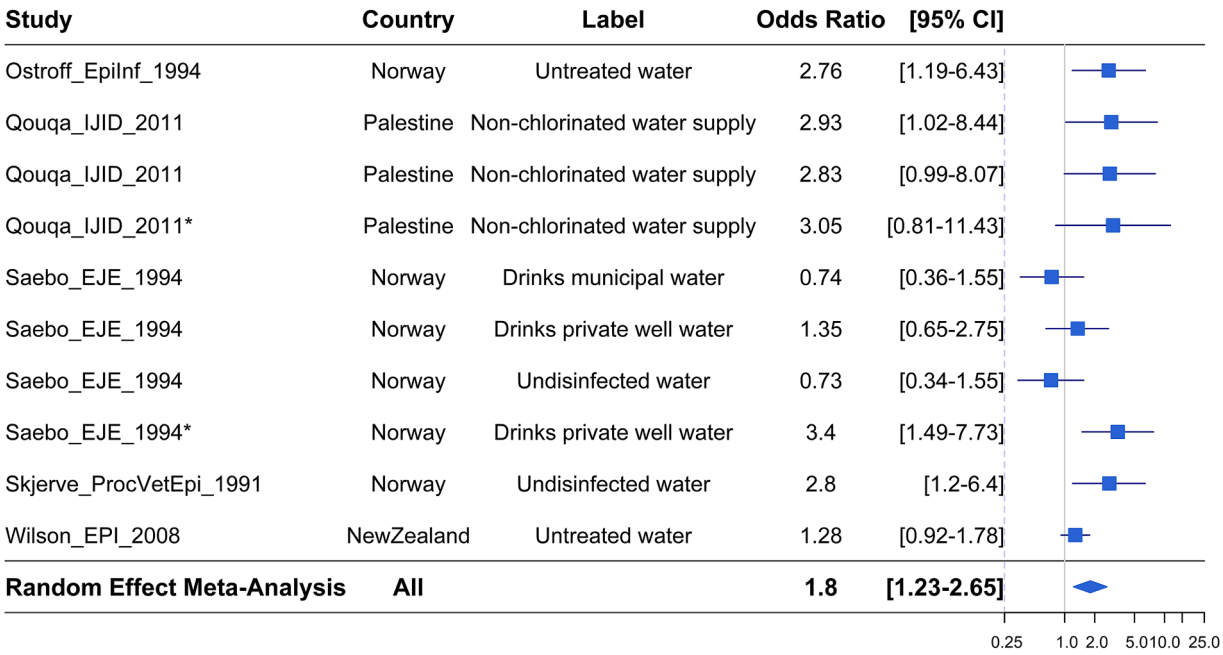

Fig. 3.. Forest plot of the associations of sporadic *Y. enterocolitica* infections with exposure to the category of untreated drinking water. (Legend * adjusted OR, N=10).

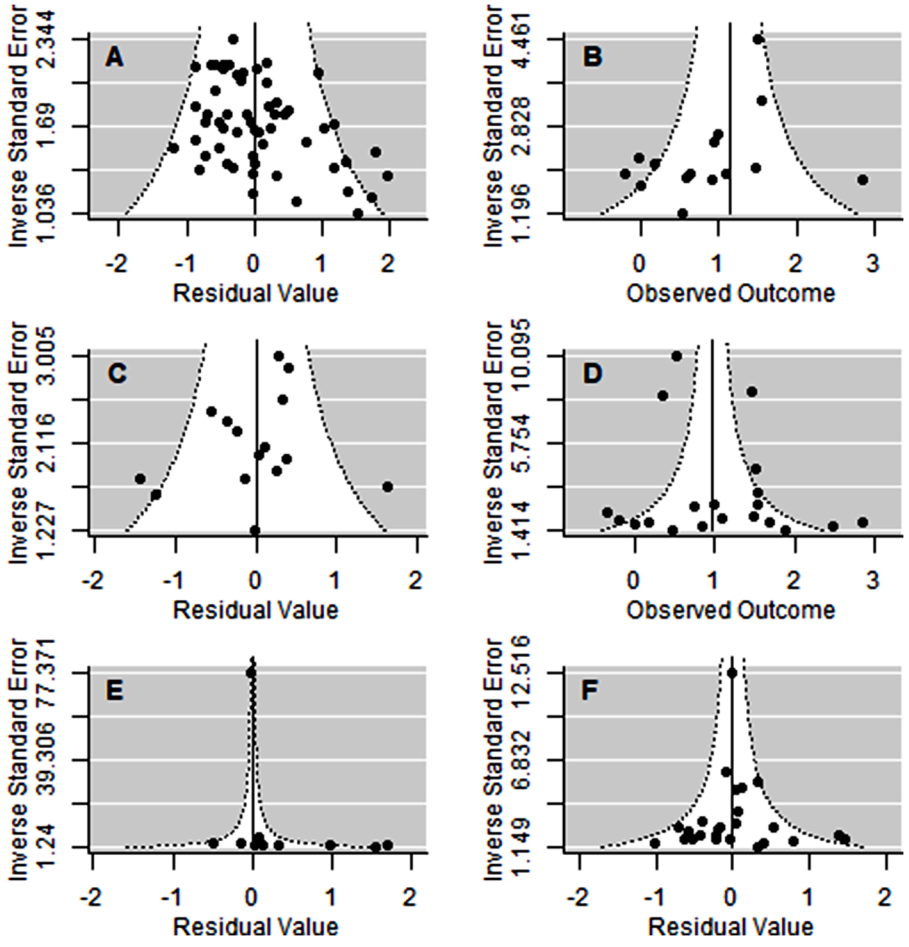

Fig. 4.. Funnel plots of studies investigating categorized risk factors. A) Food in mixed, B) Food in children, C) Meat in children D) Meat in mixed E) Composite (Fast food) and F) Handling (cooking).

analysis revealed that who travelled recently had no significantly higher (OR=2.947; 95% CI: 0.920 – 9.438) probability of getting infected with sporadic *Y. enterocolitica* infections that people who did not travel.

2.6. Risk factors associated with food-related transmission pathways

The studies explore a wide range of foods and food preparation/consumption practices (e.g. hygiene, cooking, and place of consumption). For the mixed population and children, within main large food categories, meat was the only significant risk factor (Table 2). Among meats, pork presents the highest risk factors (Table 3). The risk appears to be higher for children (overall OR=3.416; 95% CI: 1.893 – 6.16) than for mixed population (overall OR=1.995; 95% CI: 1.793 – 2.219). Two other sub-categories, that is ready-to-eat (RTE) foods (overall OR=1.096; 95% CI: 1.010 – 1.190) and composite dishes - fast food (e.g. sandwiches) (overall OR=1.198; 95% CI: 1.097 – 1.308), were also found to be associated with sporadic *Y. enterocolitica* infections but with considerably lower OR values. The consumption of raw or undercooked pork increased the odds of acquiring *Y. enterocolitica* infections by a factor of 4.215 (Table 4).

For most of the meta-analytical models reported in Tables 2, 3 and 4, the statistical tests indicated the absence of potential significant publication bias is above 5%. Exceptions were observed in partitions related to meat and pork in both mixed and children population (Tables 2 and 3), fast food in children (Table 3), and the effect of meat handling (Table 4). For better assessing the publication bias (above 5%), the funnel plot for those models is given in Fig. 4. For all of them, they were an asymmetry, and a lack of non-significant studies with smaller ORs, that could lead to OR overestimation. Moreover, the intra class correlation I^2 indicates, in all Tables, a high heterogeneity (<75%). However, residual between-study heterogeneity (p-value often below 0.05 for Q or QE) was observed for the data partitions.

3. Discussion

In this study, the aim was to synthesize data produced by published case-control studies. The weight on common factors associated with sporadic *Y. enterocolitica* infections, among them the relative importance of host-related factors, contact with animals and the environment, as well as food-related factors have been characterized. The results of the case-control surveys confirm the importance of the pig reservoir and of the practices of eating pork meat (raw or undercooked). Indeed pigs are the main carriers of *Y. enterocolitica*(Drummond et al., 2012). Moreover, the main biotype isolated in pork, that is biotype 4 (Raymond et al., 2018) matches with the most common biotype isolated in sporadic cases. Despite this association, it should be noticed that consumption of raw, undercooked pork, is rarely associated with outbreaks (Grahek-Ogden et al., 2007; Self et al., 2017). The situation is the opposite for vegetables and milk products. Both food categories were not identified as risk factors in the meta-analysis (see Appendix 2), although several outbreaks have been associated to these food products, especially for vegetables, in recent years (Espenhain et al., 2019; Konishi et al., 2016; MacDonald et al., 2012).

Untreated drinking water was also identified by the meta-analysis as a risk factor for sporadic *Y. enterocolitica* infections. This finding is also confirmed by epidemiological analysis of some outbreaks that were related to the contamination of food products by untreated drinking water contaminated by *Y. enterocolitica*(Ackers et al., 2000; Tacket et al., 1985).

Playground attendance was found to be a risk factor for children by the meta-analysis. This finding is somewhat in contradiction with the results from literature where *Y. enterocolitica* strains isolated in the environment are mainly non-pathogenic strains (Le Guern et al., 2016).

It's important to note that all the 14 studies focused on *Y. enterocolitica*. None of them integrated cases of sporadic *Y. enterocolitica* infection associated to other species, especially *Y. pseudotuberculosis*. This latter is thought to have close ecology with *Y. enterocolitica* and is regularly implicated in foodborne outbreaks (Pärn et al., 2015; Rimhanen-Finne et al., 2009). Specific case-control studies would help to confirm that risk factors also hold for other enteropathogenic *Yersinia* species.

A potential difficulty to interpret the results of the meta-analysis is related to the relative importance of biotypes/serotypes in sporadic cases according to the different continents or the different period. Pathogenic *Y. enterocolitica* strains belong to biotypes 1B, 2, 3, 4 and 5, while biotype 1A is currently considered non-pathogenic, although its association with diarrheal forms is still debated (Huovinen et al., 2010). Although bioserovar 4/O:3 is the most commonly identified type world-wide in human cases (Hunter et al., 2019; Le Guern et al., 2016; Strydom et al., 2019), some particularities can be identified. For example, biotype 2 has recently emerged as the most common biotype causing yersiniosis in New Zealand (Strydom et al., 2019). In the same way, biotype 1B was the most common biotype in the 1980s for US while now biotype 4 is the most commonly isolated biotype (Savin et al., 2018).

Another limitation of the meta-analysis is related to the origin of the studies. Most of the case-control studies included in the meta-analysis came from Europe, whereas this pathogen is also present in other continents (Duan et al., 2017; Lucero-Estrada et al., 2020). Case-control studies from other continents would help to refine our conclusions.

Several sub-typing methods have been developed for outbreak investigation (Strydom et al., 2019), such as biotyping, serotyping, PFGE, MLST and MLVA (Mughini-Gras et al., 2019). These methods have been used in the context of outbreak investigations, but they have never been used as input of source attribution models for sporadic cases of yersiniosis. Frequency-matching models for source attribution could infer the most likely sources of human sporadic cases by comparing their subtype frequencies, weighted by factors like prevalence in these sources and the human exposure to them.

In the same way, the application of WGS methods was until recently limited to outbreak investigations (Espenhain et al., 2019; Inns et al., 2018). The recent publication of the *Yersinia* cgMLST schema (Savin et al., 2019) will help to apply population structure models or machine learning approaches for estimating the attribution of sporadic yersiniosis cases to the potential sources.

4. Conclusion

The results of this meta-analysis confirm the importance of pork and untreated drinking water for sporadic *Y. enterocolitica* infections. The study also stresses the role of other routes than food, such as environmental and animal contact. The published case-control studies included this meta-analysis are stored in a database, which will be updated with other relevant studies published in the future.

To refine these results, risk factors should be investigated by *Y. enterocolitica* biotypes. Such investigations, together with specific studies dedicated to *Y. pseudotuberculosis,* could allow to identify species or sub-type source-specific risk factors and to infer the underlying transmission pathways.

CRediT authorship contribution statement

Laurent Guillier: Writing - original draft. **Philippe Fravalo:** Writing - review & editing. **Alexandre Leclercq:** Writing - review & editing.

Anne Thébault: Methodology, Formal analysis, Visualization. **Pauline Kooh:** Methodology, Project administration. **Vasco Cadavez:** Methodology, Investigation, Formal analysis. **Ursula Gonzales-Barron:** Methodology, Investigation, Formal analysis, Writing - review & editing.

Declarations of Competing Interest

The authors declare no conflict of interest.

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Appendix

Appendix 1:List of risk factors used for meta-analysis of food-borne pathogen

Table A1
Categorization scheme of main risk factors defined for transmission of foodborne diseases (from Gonzales-Barron et al., 2019).

Risk factors	Sub-categories
Environnement	Day care attendance
	Farm environment
	Forestry
	Playground
	Recreational water
	Untreated drinking water
	Waste water
Animals	Pets
	Farm animals
	Flies/rodents
	Occupational exposure
	Wild animals
Host-specific	Antiacids
	Blood Transfusion
	Breastfeeding
	Chronic diseases
	Malnutrition
	Immunocompromising conditions
	Other medical conditions
Person-to-person	Contact in household
	Contact in the community
	DrugIV
	Injection/blood contact
	Occupational exposure
	Venerian transmission
Poor handwashing/handling	
Poor personal hygiene	
Travel	Abroad
	Any
	Inside
Food	See Table A2

Table A2
Categorization scheme of food risk factors defined for transmission of foodborne diseases (from Gonzales-Barron et al., 2019).

Category	Subcategory
Beverages	Water
Composite	Dishes
	Fast food
	RTE composite
Dairy	Cheese
	Fats
	Milk
	Milk formula
	Powder
	Raw milk
	Undefined
	Raw dairy
	RTE Dairy
Eggs	Egg products
	Eggs
	Raw eggs
	Undercooked eggs
Meat	Beef
	Undercooked beef
	Other red meats
	Others
	Pork and other red meats
	Poultry
	Undercooked poultry
	Processed meat
	BBQ meat
	Raw meat
	RTE meat
	Pork
	Undercooked pork
Produce	Fruits
	Spices
	Vegetables
	Unwashed produce
Seafood	Molluscs
	Undefined
	Raw seafood
	RTE seafood
BBQ food	
RTE food	

Appendix 2:Non-significant results or isolated study

Table A3
Main risk factors.

Population	Risk factor	Pooled OR [95% CI]	N/n*
Travel			
Mixed	Travel Abroad	2.947 [0.920 - 9.434]	3/5
Host-specific			
Children	Malnutrition	4.782 [2.730 - 8.378]	1/4
Animals			
Mixed and children	Pets	1.219 [0.809 - 1.838]	4/6
	Wild animals	1.734 [1.305 - 2.304]	1/3
	Farm animals	0.834 [0.200 - 3.472]	1/6
Environment			
Mixed	Farm environment	1.158 [0.552 - 2.427]	2/3
	Wastewater	2.458 [1.155 - 5.233]	1/2
Food			
Mixed	Composite	1.326 [0.766 - 2.296]	3/9
	Produce	1.202 [0.659 - 2.193]	1/11

*N/n Number of studies/number of OR

Table A4
Disaggregated risk factors.

Risk Factor	Risk factor precise	Population	Pooled OR [95% CI]	N/ n*
Meat	Beef	Mixed	0.734 [0.636 - 0.847]	2/5
	Other red meats		0.9793 [0.896 - 1.070]	2/7
	Others		1.310 [0.893 - 1.920]	1/5
	Poultry		1.564 [0.787 - 3.106]	1/2
	Processed meat		1.033 [0.970 - 1.101]	4/7
Meat	Processed meat	Children	2.449 [1.232 - 4.867]	1/7
Composite	Dishes	Mixed	1.306 [0.793 - 2.149]	3/6

*N/n Number of studies/number of OR

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