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The epidemiology of published norovirus outbreaks: a systematic review of risk factors associated with attack rate and genogroup

J. E. Matthews[1,*], **B. W. Dickey**[1,*], **R. D. Miller**[1], **J. R. Felzer**[1], **B. P. Dawson**[1], **A. S. Lee**[1], **J. J. Rocks**[1], **J. Kiel**[1], **J. S. Montes**[1], **C. L. Moe**[1], **J. N. S. Eisenberg**[2], and **J. S. Leon**[1]

[1]Hubert Department of Global Health, Emory University Rollins School of Public Health, Atlanta, GA, USA

[2]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA

SUMMARY

The purpose of this study was to examine global epidemiological trends in human norovirus (NoV) outbreaks by transmission route and setting, and describe relationships between these characteristics, viral attack rates, and the occurrence of genogroup I (GI) or genogroup II (GII) strains in outbreaks. We analysed data from 902 RT-PCR-confirmed, human NoV outbreaks extracted from a systematic review of articles published from 1993 to 2011 and indexed under the terms “norovirus” and “outbreak.” Multivariate regression analyses demonstrated that foodservice and winter outbreaks were significantly associated with higher attack rates. Food- and waterborne outbreaks were associated with multiple strains (GI+GII). Waterborne outbreaks were significantly associated with GI strains, while healthcare-related and winter outbreaks were associated with GII strains. These results identify important trends for epidemic NoV detection, prevention, and control.

INTRODUCTION

Noroviruses (NoV)—non-enveloped, single-stranded RNA viruses—are a leading cause of non-bacterial gastroenteritis and are responsible for an estimated 218000 deaths each year in children under five and 1.1 million hospitalizations worldwide [1]. NoV infection has an average incubation period between 24 and 48 hours and average illness duration between 12 and 60 hours [2]. NoV infection may induce vomiting, diarrhoea, mild fever, abdominal cramping, and nausea in infected individuals. The primary mode of transmission is faecal-oral and occurs through ingestion of contaminated water, consumption of contaminated food, or direct contact with environmental surfaces or infected persons. As few as ten viral particles can cause infection (ID_{50}=18 viruses) [3], and NoV can persist in the environment even after disinfection (reviewed in [4], and [5]). NoV are genetically classified into five genogroups, of which GII, GI, and GIV (rarely), in order of greatest to lowest numbers, are responsible for human outbreaks [6]. Within the GII genogroup, GII.4 strains are responsible for most human NoV outbreaks, including pandemics [4].

Despite the ability to detect and classify NoV through antibody-based assays (since 1985) and genomic amplification assays (since 1992), many fundamental questions regarding NoV

Corresponding Author (and Requests for Reprints): Juan S. Leon, Emory University, Hubert Department of Global Health, Mailstop 1518-002-7BB, 1518 Clifton Road NE, Atlanta, GA 30322, USA, Tel: +1-404-727-7443, juan.leon@emory.edu.
*Both authors contributed equally to this work

outbreak characteristics have either been incompletely addressed or remain unanswered from analysis of surveillance data. To be reliable sources of data for epidemiological research, surveillance systems rely on management teams (e.g. restaurants, hotels) and healthcare administrators (e.g. hospitals, long-term care facilities) to consistently notify public health authorities when they suspect an infectious disease outbreak has occurred, so that appropriate follow-up activities (e.g. laboratory confirmation, epidemiological study, etc.) can be conducted. Primary cases can then be defined as those individuals suspected to be infected by a common vehicle and confirmed via a laboratory or clinical diagnosis. Primary attack rates can then be defined as the proportion of individuals who become ill following direct contact with a person or object infected with NoV divided by the number of individuals at risk. By virtue of their large sample size (more outbreaks), large studies of norovirus outbreak epidemiology derived from such surveillance data [7, 8] are able to provide highly precise measures of effect (characterized by narrower error intervals).

In addition to these large norovirus epidemiological studies, other published studies describe data from: 1) a subset of outbreaks that were reported to or by public health authorities for additional genotyping [9–12], 2) outbreaks that have been aggregated as part of smaller, more focused NoV surveillance networks (e.g. Vessel Sanitation Program for norovirus outbreaks on cruise ships) [13], 3) active surveillance [14], or 4) form the foundations of pilot NoV surveillance networks in some countries, such as France [15] or Switzerland [16]. In general, these studies suggest that a majority of reported NoV outbreaks take place in healthcare facilities and foodservice settings [9–12, 15, 16]. In addition, food- and waterborne outbreaks have often been associated with high attack rates [11, 16]; however, while a number of studies characterize food-associated outbreaks, compared to outbreaks in other settings, as having smaller numbers of primary cases and persons at risk [9–11], some studies suggest contradictory conclusions [14]. Furthermore, a higher proportion of GII strains, as compared to GI strains, were reported in a majority of outbreaks across several studies [9, 11, 13, 15, 17] and were commonly associated with healthcare settings [9, 11, 15]. In general, GII.4 outbreaks were associated with lower attack rates [17]. Knowledge gaps from previous studies include: 1) lack of statistical comparison of the number of cases, persons at risk, or attack rate across outbreak settings and modes of transmission; 2) limited analyses of attack rate differences between and among the NoV genogroups that most commonly infect humans, GI and GII; and 3) infrequent use of statistical adjustment or multivariate modeling to study the influence of multiple variables simultaneously on an outcome.

Based on data abstracted from a systematic review of published NoV outbreak reports, this investigation seeks to address these knowledge gaps in NoV outbreak epidemiology and expand on previous research by exploring the relationship between potential risk factors for NoV outbreaks worldwide using multivariate models.

METHODS

Article Identification

Literature searches for the terms “norovirus” and “outbreak” were performed in PubMed, EMBASE, and Web of Knowledge. MeSH terms were expanded in PubMed when available and Boolean operators were used to include all possible term forms. The complete search strategy is included as Supplementary Material [Appendix S1].

Article Screening

Our literature search identified 2435 non-duplicate articles [Figure 1]. Two reviewers independently assessed each article for inclusion. The inclusion criteria required that articles

1) be published in an article format (e.g. citations of conference abstracts were excluded), 2) be published entirely in English, 3) describe human NoV outbreaks, and 4) have at least one case from each NoV outbreak confirmed by RT-PCR. Furthermore, the articles were required to have explicitly stated the number of primary cases (the article was excluded if the number of NoV-positive stools was reported instead of the number of primary cases). The exclusion criteria eliminated articles that documented sporadic cases of NoV or were published prior to the development of RT-PCR methodology for NoV detection in 1992. Discrepancies between each pair of reviews were resolved by consensus or a third investigator. Rather than impose a uniform case definition on the articles, we adopted each author's case definition. Relevant articles were allowed to contain information on more than one outbreak and data was abstracted separately for each outbreak. However, outbreaks reported in multiple publications were only recorded once.

NoV Outbreak Database

A standardized Epi Info™ survey (version 3.5.1) was used to abstract data on as many as 74 variables (when available) into a Microsoft Access database. These variables included, but were not limited to: mode of transmission (described below), vehicle (person or object infected or contaminated with NoV that promotes transmission of virus to healthy individuals or contamination of additional objects or surfaces with virus), genetic classification (genogroup and genotype/cluster), outbreak beginning and end dates, location (described below), outbreak setting (described below), incubation period (length of time between viral infection and symptom presentation), illness duration, case ages, number of primary cases and persons at risk (described below), primary attack rates, and description of any action taken to stop the outbreak.

During data abstraction, calculations were limited to addition or subtraction (e.g. adding staff and guest cases to generate a total primary case number for a hotel outbreak). Reported numbers of laboratory confirmed and clinically identified primary cases were also combined. Data were cleaned using SAS™ version 9.2 (SAS Institute, Cary, NC, USA). Outbreak seasonality was derived from the month of occurrence and the hemisphere of the affected country. Modes of transmission were categorized as follows: foodborne (e.g. consumption of contaminated shellfish or foods contaminated during production or preparation by an infected foodhandler), waterborne (e.g. drinking or recreational water), person-to-person (direct contact with infected vomitus or other aerosolized virus particles), and environmental (direct contact with contaminated surfaces). Outbreak settings were categorized as follows: foodservice (e.g. restaurants), healthcare (e.g. hospitals, long-term care facilities, psychiatric institutions), leisure (e.g. vacations, cruises, hotels, recreational activities), school/daycare (e.g. schools, daycare facilities, universities), and other (e.g. residential, community-wide outbreaks, military, and prison settings). Outbreaks were classified as GI or GII if the associated strains were identified exclusively as belonging to one genogroup or the other; outbreaks associated with GI and GII strains combined were classified accordingly, as long as one strain from the outbreak was identified as belonging to GI and another was identified as belonging to GII. To avoid counting an outbreak more than once, an outbreak associated with strains from multiple genogroups was not classified as belonging to GI individually or GII individually. To include the maximum number of outbreaks in the analysis, an algorithm was constructed in SAS to calculate number of persons at risk for direct infection with NoV (primary cases ÷ primary attack rate) and primary attack rate (primary cases ÷ persons at risk) for outbreaks from which those variables were not abstracted.

Statistical Analysis

All analyses were conducted with SAS™ version 9.2. Analyses of primary attack rate were restricted to outbreaks that simultaneously contained data for all three of the following variables: primary cases, persons at risk, and primary attack rate. Analyses of genogroup were restricted to outbreaks that contained data on whether the outbreak was a GI individually, GII individually, or GI and GII combined outbreak. Continuous variables were non-normal even after transformations and therefore were expressed as the median and interquartile range (IQR). Multiple groups of continuous data were compared with a Kruskal-Wallis test and post-hoc adjustments for multiple comparisons using Dunn's test [18]. Multiple groups of categorical data were compared by first analysing the groups with an overall chi-square test. Post-hoc two-by-two chi-square analyses with Tukey-style adjustment for multiple comparisons were subsequently performed using the COMPPROP macro for SAS™ [19].

Independent variables included in the multivariate regression models [primary attack rate (linear), occurrence of GI or GII strains in outbreaks (logistic)] were determined *a priori*: mode of transmission, outbreak setting, season, outbreak year, action taken in response (as described in article), genogroup (linear), and primary attack rate (logistic). Multivariate regression models only included outbreaks that had values for *all* variables in the models. One model excluded outbreaks with more than one transmission route, while another considered these multiple transmission outbreaks as separate, independent outbreaks—wherein each outbreak was associated with a single transmission route. An interaction assessment was not performed because of the large number of pairwise interaction terms, low statistical power to evaluate all such interactions, and the potential for instability in model estimates.

For linear models, collinearity was considered to be present if the variance inflation factor associated with any covariate exceeded ten. For the logistic models, multicollinearity was considered to be present if any condition index obtained using the COLLIN macro for SAS™ [20] exceeded 15. Collinear variables were removed from all adjusted models. Penalized maximum likelihood estimation techniques [21] were employed after examination of the full logistic model revealed a quasi-complete separation of data points (due to few observations in some categories of one or more stratified covariates).

RESULTS

We analysed 902 eligible outbreaks. These outbreaks occurred between December 1983 and March 2010 and were extracted from 250 articles published between December 1993 and May 2011 [Figure 1 and Supplementary Material, Appendix S2]. Of the 896 outbreaks documenting year of occurrence, 71% occurred between 2000 and 2010. More than 90% of outbreaks occurred in the northern hemisphere and 45% took place during the winter.

Transmission Route and Setting

Transmission route data was available for 565 outbreaks; 89 (16%) involved two or more modes of transmission. Multiple transmission outbreaks were replicated and segregated into their individual component modes of transmission, resulting in 666 observations for the transmission route sub-analysis [Table 1]. Setting data was abstracted from 830 outbreaks [Table 1]. Reported outbreaks were most commonly attributed to foodborne transmission (362/666, 54%) and foodservice settings (294/830, 35%), whereas the fewest number of outbreaks was associated with environmental transmission (60/666, 9%) or reported in school or daycare settings (80/830, 10%). As described in the methods, settings were consolidated to enhance statistical power, but within each setting, there were subcategories

that comprised more than 15% of the reported setting. “School/Daycare” was comprised of school (64/80, 80%) and daycare (16/80, 20%) outbreaks. Similarly “Healthcare” was comprised of hospitals (107/225, 48%) and long-term care facilities (112/225, 50%). “Other” included private homes (30/91, 33%), community-wide outbreaks (20/91, 22%) and military settings (15/91, 16%). In general, outbreaks due to foodborne transmission or foodservice setting were significantly associated with the lowest number of primary cases and persons at risk, but were significantly associated with the highest attack rate when compared to other modes of transmission or outbreak settings. In addition, waterborne transmission attack rates were significantly higher than those associated with person-to-person or environmental transmission. Healthcare-related outbreaks were significantly associated with fewer primary cases and had the lowest attack rates.

We assessed 580 outbreaks that recorded information on primary attack rate, ranging from less than 1% to 100%, for significant bivariate relationships. Food- and waterborne outbreaks, as well as outbreaks in foodservice settings and outbreaks associated with both GI and GII strains, had significantly higher attack rates, when compared to their referent categories [Table 2]. By contrast, healthcare-related and GII cluster four (GII.4) NoV outbreaks, as well as outbreaks in which authors described a corrective action, had significantly lower attack rates.

In the multivariate linear regression model where multiple transmission outbreaks were excluded [Table 2], or where they were included in a model as an extra dummy variable (data not shown), no covariates were significantly associated with a higher or lower attack rate. However, winter season was borderline significant in the model where multiple transmission routes were classified as an extra dummy variable ($p = 0.056$, data not shown). In the model that included multiple transmission routes, where we classified outbreaks of more than one mode of transmission as multiple, independent outbreaks of a single transmission type (see Methods), outbreaks in foodservice settings and in the winter were associated with higher attack rates, when compared to their referent categories.

To assess whether additional covariates were significant if the power (sample size) of the models was increased, we included outbreaks that lacked data for the “setting” variable and found that, in either adjusted model, foodborne outbreaks were associated with higher attack rates, when compared to their referent categories (data not shown). In the model where outbreaks with multiple modes of transmission were included, winter outbreaks were also associated with higher attack rates (data not shown). When we included outbreaks that lacked data for the “mode of transmission” variable in either adjusted model, outbreaks in foodservice settings had significantly higher attack rates (data not shown). In addition, the “outbreak year” variable had a significant negative relationship with attack rate—outbreaks that occurred more recently were associated with lower attack rates (data not shown). Furthermore, in the model where outbreaks with multiple modes of transmission were included, spring outbreaks were associated with higher attack rates (data not shown).

Genogroup, Transmission, and Setting

We analysed 754 outbreaks that had genogroup data and 581 that had cluster-level data. Compared to outbreaks associated with GI strains (99/754, 13%) and multiple strains (GI +GII, 92/754, 12%), outbreaks associated with GII strains had the highest proportion (563/754, 75%). GII.4 was reported in one third of outbreaks associated with a single strain (genogroup and cluster).

In general, GI, compared to GII, outbreaks were significantly more likely to be associated with waterborne transmission [Table 3 and Table 4 (adjusted OR [aOR]: 0.19, 95% confidence interval [CI] 0.05–0.67)]. A significantly smaller proportion of water- and

foodborne outbreaks was associated with GII (including GII.4) strains, when compared to other modes of transmission [Table 3]. However, a significantly higher proportion of water- and foodborne outbreaks was associated with multiple strains (GI+GII) appearing simultaneously. GII, compared to GI, outbreaks were significantly associated with healthcare setting [Table 3 and Table 4 (aOR: 33.67, 95% CI: 1.76–644.18)]. The 95% CI around the healthcare setting aOR was large because all 47 healthcare-related outbreaks in the model were associated with GII strains. Similarly, a higher proportion of NoV outbreaks in healthcare-related and leisure settings was associated with GII.4 strains, compared to other settings [Table 3]. GII, compared to GI, outbreaks were also significantly associated with winter compared to fall [aOR: 5.34, 95% CI: 1.94–14.73, Table 4]. To assess whether additional covariates were significant if the power (sample size) of the models was increased, we included outbreaks lacking either setting or transmission data in the fully adjusted models but found no additional significant associations beyond those described (data not shown).

DISCUSSION

The goal of this analysis was to examine relationships between primary attack rate, genogroup, mode of transmission, outbreak setting, and other NoV outbreak characteristics. In general, we found the number of primary cases and persons at risk was significantly lower in outbreaks related to food and healthcare settings. Attack rates were significantly higher in outbreaks related to food, water, and in the winter. By contrast, the attack rate was lower in healthcare-related outbreaks. Regarding genogroup, outbreaks in healthcare settings and in the winter were more likely to be associated with GII strains, while waterborne outbreaks were more likely to be associated with GI strains. These results were largely consistent with published literature [9, 11, 14, 15].

Our finding that food-related outbreaks were associated with the fewest cases and persons at risk [Table 1] suggests that viral transmission within a confined space, such as a restaurant, may limit the primary cases and persons at risk to only those persons sharing that space. By contrast, the number of primary cases or persons at risk may be larger, compared to food-related outbreaks, in waterborne outbreaks in which contaminated drinking water is distributed throughout a community or person-to-person outbreaks where an infected person becomes a mobile source of exposure. Improved global surveillance networks for foodborne outbreaks, such as FoodNet in the United States [22], the NoroNet network in Europe [8], and OzFoodNet in Australia [23], may allow for the detection of smaller outbreaks.

Previous research by Kaplan, *et al.* [14] supports our observation that food- and waterborne outbreaks have significantly greater attack rates when compared to person-to-person and environmental outbreaks [Tables 1, 2]. Food and waterborne outbreaks may have greater attack rates due to: 1) consumption of higher infectious doses of NoV, and 2) more accurate identification of persons at risk (i.e. all persons eating a food item versus all persons who may have had contact with an infected person). As mentioned previously, active monitoring by targeted surveillance systems may lead to more accurate detection and classification of NoV food- and water-related outbreaks [22, 24]. In a manner similar to other published reports [25, 26], our analysis also indicated that outbreaks in healthcare settings were associated with low attack rates [Table 1]. Several factors may account for this finding, including the limited mobility of infected persons in hospitals and nursing homes, requirements in the United States for active hospital infection surveillance, the likelihood of more interventions associated with person-to-person spread within the institutional environment, and the implicit financial and quality improvement incentives to encourage healthcare facilities to reduce the incidence of nosocomial NoV outbreaks [26].

In contrast to Kroneman, *et al.* [27]—who did not observe a significant multivariate association between season and genogroup—we observed that outbreaks in the winter were more likely to be caused by GII strains than outbreaks in the fall [Table 4]. As mentioned previously, the clustering of people indoors during seasonal cold weather, combined with an absence of herd immunity to circulating NoV strains [28, 29], may facilitate person-to-person NoV transmission. We also found that GII strains, particularly GII.4, were more likely to be present among outbreaks that occurred in healthcare settings. A higher proportion of hospitalized patients may be infected with NoV in winter because, in winter, hospitals may receive a larger intake of patients (e.g. respiratory diseases), which may facilitate the spread of NoV within an enclosed environment [7]. Furthermore, elderly populations and patients with pre-existing conditions may be more susceptible to GII.4 strains, which have been shown to mutate quickly [9, 27]. A 2006 study by Chan, *et al.* suggests that individuals with NoV GII infection may shed higher concentrations of virus than individuals with NoV GI infection [30]. Recent findings published by Lee, *et al.* suggest that the elderly and persons with pre-existing conditions may shed NoVs for longer periods of time than healthy young people [31]. Therefore, shedding higher concentrations of virus for longer periods of time may greatly favor transmission of GII strains over GI strains.

Finally, we observed that GI strains were significantly more likely to have been transmitted via water than by other routes of transmission. While the majority of strains implicated in foodborne, person-to-person, and environmental outbreaks belonged to GII [Table 3], waterborne strains were more likely to belong to GI [Tables 3, 4]. This finding is consistent with previous research [32]. While previous work suggests that a representative GI strain is less stable on surfaces than a representative GII strain [33], it is possible that GI strains are more stable in water than GII strains. GI NoV stored in groundwater was still infectious in human volunteers after two months [34] and GI NoV RNA stored in groundwater was still detectable by RT-PCR after 588 days [35].

Limitations and Strengths

There were three main limitations to this study. First, as is the case with many systematic reviews, our study was influenced by publication bias. We extracted data of several reports from active surveillance that were published. Publications were more likely from outbreaks with novel findings than small, relatively common outbreaks (e.g. healthcare-related settings). However, most infectious disease outbreaks are reported by passive surveillance. Passive surveillance has its own biases. Outbreak data collected may not be as comprehensive in passive versus active surveillance. Some outbreaks may not be recognized because illness is mild or because cases disperse (e.g. restaurant). In contrast, outbreaks may be recognized when cases are in communication with each other (e.g. wedding). Publication bias also resulted from the overrepresentation of outbreak data from five countries (Japan, United States, Sweden, United Kingdom, Netherlands) that accounted for approximately two-thirds of the reported outbreaks. Care should be taken when generalizing these results to countries with limited or extensive surveillance. For example, some countries may only be able to investigate outbreaks in one setting (e.g. foodservice or healthcare-related) or may have better surveillance of food- and waterborne outbreaks because it is easier to implicate a contaminated food item or water source than an environmental or person-to-person source.

Second, because we treated outbreaks with more than one mode of transmission as multiple, independent outbreaks of a single transmission type, we increased the effective sample size in these models and therefore some non-significant variables may have become significant. These findings may still be biologically valid but additional analyses of data from outbreaks with multiple transmission routes are needed to validate these findings. Third, as our data came from different authors, all outbreaks did not have the same variables. This limited the

number of analysed outbreaks and may have increased the likelihood of misclassification bias (e.g. an outbreak that reported only genogroup-level information would not have been analysed as a GII.4 outbreak).

There were three key strengths to this analysis. First, we employed a rigorous study protocol that required validation by at least two individuals following article selection and data abstraction. Second, this analysis incorporates a greater number of countries than any other review of published NoV outbreak studies [7, 9, 27]. Third, the size of our database and multivariate modeling allowed us to control for a variety of variables. Furthermore, publication bias likely minimally influenced the multivariate analysis identifying factors associated with either GI or GII outbreaks [Table 4] because an outbreak was neither any more likely nor any less likely to be published simply because it was associated with a GI or a GII strain.

Implications

There are several important implications from this study. First, point source outbreaks (e.g. food) were associated with the highest illness burden, primary attack rates, and proportion of outbreaks, and were more likely to be caused by strains from multiple genogroups. These results suggest that several primer sets should be used in the detection of NoV from point source outbreak specimens. Second, healthcare settings were associated with low primary attack rates, which is likely due to effective infection control practices in healthcare facilities. Third, NoV outbreak attack rates may fluctuate by seasons and one NoV genogroup may predominate over another in outbreaks, particularly in the winter.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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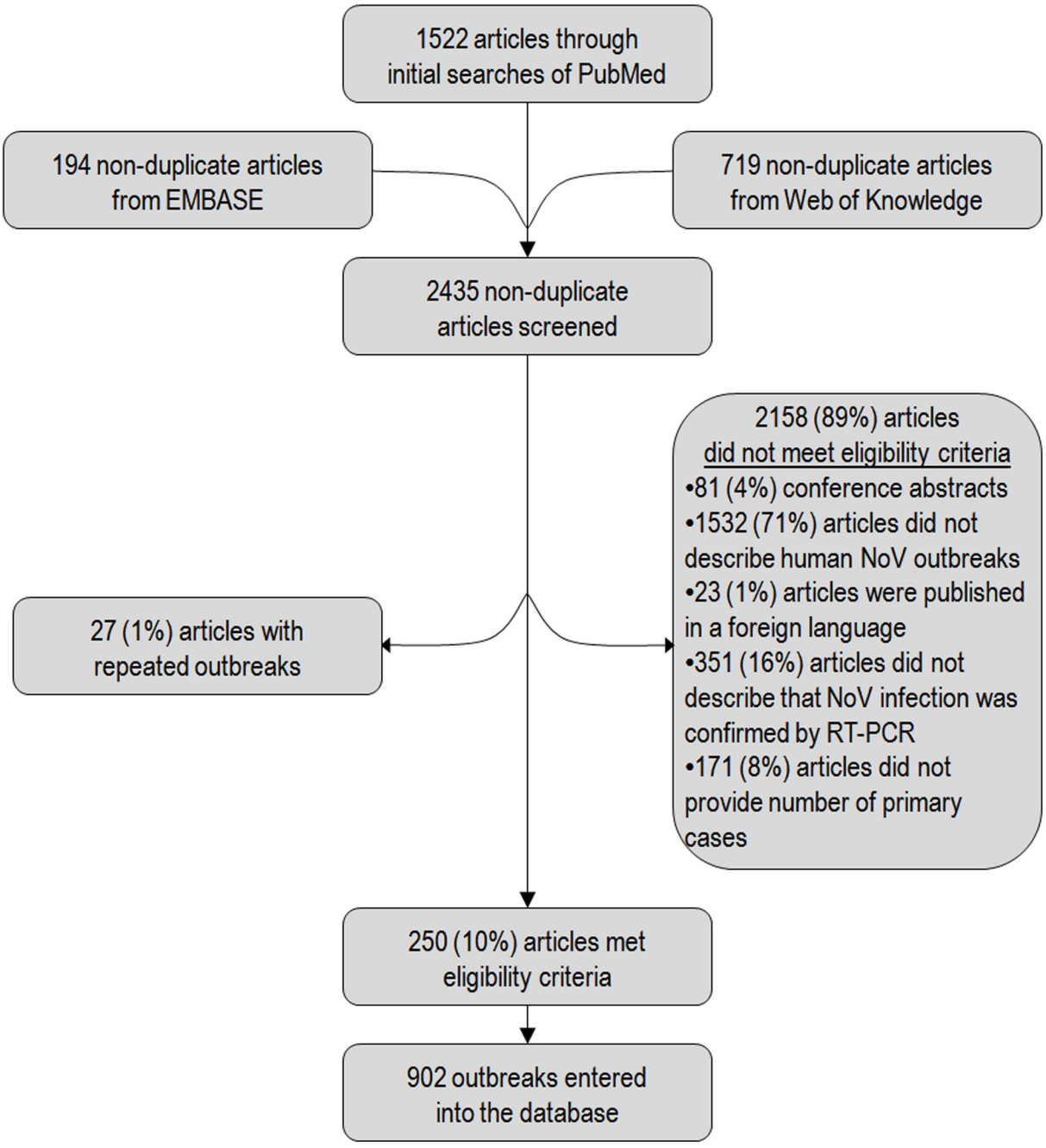

Figure 1.
Flow diagram of searches, screening, and selection of eligible articles for creation of NoV outbreak database. The 250 articles meeting inclusion criteria contained 900 outbreaks published between December 1993 and May 2011. Outbreaks spanned from December 1983 to March 2010. Arrows indicate the temporal order of the steps represented in the gray rectangles.

Table 1

Comparative analysis of the number of primary cases, persons at risk and primary attack rate by mode of transmission and setting.

Variable	Outbreaks n (%)	Analysed Sample*	Primary Cases Median (IQR)	Persons at Risk Median (IQR)	Primary Attack Rate Median (IQR)
Transmission†‡					
Foodborne	362 (54)	252	20 (9–55)	50 (18–150)	50% (31–71%)
Person-to-Person	174 (26)	118	69 (36–175)§	262 (108–1888)§	27% (12–46%)§‖
Waterborne	70 (11)	43	61 (40–175)§	160 (81–672)§	38% (28–64%)
Environmental	60 (9)	47	108 (35–252)§	492 (135–2442)§	26% (9–41%)§‖
Total	666	460	40 (15–104)	111 (32–414)	40% (21–62%)
Setting¶					
Foodservice	294 (35)	209	15 (7–38)	33 (14–94)	53% (33–75%)
Healthcare	225 (27)	123	22 (6–53)	101 (70–200)**	20% (6–34%)**
Leisure	140 (17)	114	58 (22–158)**††	211 (80–1280)**	29% (11–48%)**††
School/Daycare	80 (10)	44	40 (13–84)**	144 (45–266)**	28% (13–46%)**
Other	91 (11)	51	58 (13–300)**††	250 (23–2500)**	36% (13–67%)**††
Total	830	541	26 (10–70)	84 (33–240)	36% (16–58%)

*Complete information was not available for all outbreaks. Summary statistics were calculated for a subset of the outbreaks, described in the "Outbreaks" column, with information on all three of the following variables: the number of primary cases, persons at risk, and primary attack rate.

†Foodborne outbreaks included those associated with NoV infection following consumption of shellfish or other foods contaminated during production or preparation by an infected foodhandler. Person-to-person outbreaks included those associated with NoV infection following direct contact with vomitus or other aerosolized viral particles. Waterborne outbreaks included those associated with ingestion of infected drinking or recreational water. Environmental outbreaks included those associated with NoV infection following direct physical contact with contaminated surfaces.

‡Up to three modes of transmission may have been listed per outbreak. Outbreaks may therefore be listed under more than one mode of transmission.

§Significantly different from foodborne transmission at $p < 0.05$.

‖Significantly different from waterborne transmission at $p < 0.05$.

¶Foodservice settings included restaurants, wedding receptions and other catered functions. Healthcare settings included hospitals, emergency rooms, clinics, psychiatric institutions, nursing homes, and assisted living facilities. Leisure settings included hotels, cruise ships, tour buses, camps, and ski lodges. School/daycare settings included primary, secondary, elementary, middle and high schools, as well as daycares, colleges, and universities. Other outbreak settings included residential, military and jail settings.

**Significantly different from foodservice settings at $p < 0.05$.

††Significantly different from healthcare settings at $p < 0.05$.

Table 2

Unadjusted and adjusted multiple linear regression coefficients modeling primary attack rate as a function of potential NoV outbreak risk factors.

Variable	Unadjusted*				Adjusted, no multiple transmission routes (n=233)			Adjusted, with multiple transmission routes (n=339)		
	Beta	Std Error	P-value	n	Beta	Std Error	P-value	Beta	Std Error	P-value
Intercept					1470.05	913.86	0.11	257.92	754.32	0.73
Transmission				309						
Foodborne	29.48†	4.11	<0.0001		10.53	7.20	0.15	5.48	3.99	0.17
Waterborne	18.18†	5.76	<0.01		13.40	8.22	0.10	7.61	5.38	0.16
Environmental	7.63	12.22	0.53		11.76	15.66	0.45	−3.38	5.29	0.52
Person-to-Person	Ref.	-	-		Ref.	-	-	Ref.	-	-
Setting				469						
Foodservice	22.07†	4.35	<0.0001		14.23	8.37	0.09	14.17†	5.96	0.02
Healthcare	−10.93†	4.62	0.02		0.68	9.35	0.94	−3.11	6.58	0.64
Leisure	0.72	4.88	0.88		−1.34	8.84	0.88	−3.01	5.92	0.61
Other	9.77	5.39	0.07		−2.61	9.28	0.78	−0.42	6.79	0.95
School/Daycare	Ref.	-	-		Ref.	-	-	Ref.	-	-
Outbreak Year	0.01	0.01	0.31	508	−0.72	0.46	0.12	−0.11	0.38	0.76
Season				475						
Winter	2.75	3.89	0.48		6.03	5.08	0.24	9.90†	3.56	<0.01
Spring	5.74	4.34	0.19		0.19	5.51	0.97	7.24	4.13	0.08
Summer	−0.47	5.09	0.93		−1.31	5.79	0.82	2.10	4.22	0.62
Fall	Ref.	-	-		Ref.	-	-	Ref.	-	-
Action to stop transmission				508						
Described in article	−8.27†	3.45	0.02		−6.53	4.46	0.14	2.61	3.16	0.41
Not described	Ref.	-	-		Ref.	-	-	Ref.	-	-
Genogroup				430						
Genogroup II	−2.83	4.26	0.51		0.33	5.35	0.95	−3.69	4.24	0.39
Both GI and GII	11.17†	5.34	0.04		5.63	6.04	0.35	−0.21	4.95	0.97
Genogroup I	Ref.	-	-		Ref.	-	-	Ref.	-	-
Genogroup, by cluster‡				362						

Variable	Unadjusted*				Adjusted, no multiple transmission routes (n=233)			Adjusted, with multiple transmission routes (n=339)		
	Beta	Std Error	P-value	n	Beta	Std Error	P-value	Beta	Std Error	P-value
GII non cluster 4	0.97	4.27	0.82							
GII cluster 4	−16.16†	4.27	0.0002							
Both GI and GII	7.66	5.29	0.15							
GI	Ref.	-	-							
Adjusted R^2						0.14			0.15	

*Unadjusted analyses excluded outbreaks with multiple modes of transmission.

†$p < 0.05$.

‡GII outbreaks with no cluster data were excluded from unadjusted model.

Table 3

Comparative analysis of NoV outbreaks associated with genogroup by mode of transmission and outbreak setting.

Variable*	GI	GII†	Both GI and GII†	Total	GII.4‡
	n (row % of total)	n (row % of total)	n (row % of total)	n (column % of total)	n (row % of total)
Transmission					
Foodborne	43 (13)§	211 (66)§	65 (20)	319 (57)	66 (26)
Person-to-Person	12 (8)§	123 (87)§//	7 (5)§//	142 (25)	69 (58)§//
Waterborne	18 (31)	22 (37)	19 (32)	59 (10)	11 (21)
Environmental	2 (4)§	40 (89)§//	3 (7)§	45 (8)	28 (68)§//
Subtotal	75 (13)	396 (70)	94 (17)	565	174 (37)
Setting					
Foodservice	41 (16)¶	176 (67)¶	45 (17)¶	262 (38)	47 (22)¶
Healthcare	7 (4)	159 (96)	0 (0)	166 (24)	105 (74)
Leisure	15 (15)¶	76 (74)¶	12 (12)¶	103 (15)	45 (51)¶**††
School/Daycare	13 (17)¶	57 (76)¶	5 (7)¶	75 (11)	13 (21)¶
Other	11 (14)	52 (65)¶	17 (21)¶**	80 (12)	22 (32)¶
Subtotal	87 (13)	520 (76)	79 (12)	686	232 (40)

*Up to three modes of transmission may have been listed per outbreak. Outbreaks may therefore be listed under more than one mode of transmission. Per cents may sum to more than 100 due to rounding.

†Includes all GII strains including those lacking a specific GII cluster designation.

‡Per cents and total excludes segment of GII strains lacking a specific GII cluster designation.

§Significantly different from waterborne transmission types ($p < 0.05$).

//Significantly different from foodborne transmission types ($p < 0.05$).

¶Significantly different from healthcare settings ($p < 0.05$).

**Significantly different from school/daycare settings ($p < 0.05$).

††Significantly different from foodservice settings ($p < 0.05$).

Table 4

Unadjusted and adjusted odds ratios modeling the likelihood of whether a GI or GII NoV strain is associated with an outbreak that is characterized by the presence of potential NoV risk factors.

Variable	Unadjusted*				Adjusted, no multiple transmission routes (n=184)			Adjusted, with multiple transmission routes (n=281)		
	OR†	95% CI		n	OR†	95% CI		OR†	95% CI	
Transmission				339						
Foodborne	0.46	0.19	1.11		2.21	0.42	11.52	1.33	0.49	3.62
Waterborne	0.10≠	0.04	0.29		0.42	0.07	2.33	0.19≠	0.05	0.67
Environmental	0.81	0.03	23.34		0.93	0.01	60.48	2.16	0.35	13.49
Person-to-Person	Ref.	-	-		Ref.	-	-	Ref.	-	-
Setting				545						
Foodservice	1.05	0.52	2.15		0.86	0.13	5.80	1.46	0.37	5.70
Healthcare	4.37≠	1.67	11.43		20.47	0.81	520.49	33.67≠	1.76	644.18
Leisure	0.83	0.35	1.96		0.93	0.13	6.55	2.77	0.70	10.98
Other	0.93	0.38	2.28		0.86	0.11	6.88	2.42	0.47	12.43
School/Daycare	Ref.	-	-		Ref.	-	-	Ref.	-	-
Season				552						
Winter	2.17≠	1.14	4.10		8.76≠	2.43	31.56	5.34≠	1.94	14.73
Spring	1.21	0.62	2.39		1.54	0.47	4.97	0.99	0.38	2.58
Summer	0.92	0.44	1.93		2.71	0.83	8.87	2.27	0.83	6.19
Fall	Ref.	-	-		Ref.	-	-	Ref.	-	-
Action to stop transmission				600						
Described in article	0.73	0.38	1.42		0.51	0.18	1.44	0.68	0.30	1.52
Not described	Ref.	-	-		Ref.	-	-	Ref.	-	-
Outbreak Year	1.00	1.00	1.00	600						
Primary Attack Rate	1.00	0.99	1.01	366	1.00	0.99	1.02	1.00	0.98	1.01

*Unadjusted analyses excluded outbreaks with multiple modes of transmission.

†Significant odds ratios (ORs) greater than one represent that the odds an outbreak was caused by a GII strain were greater than the odds an outbreak was caused by a GI strain.

≠$p < 0.05$.