Global Prevalence of Asymptomatic Norovirus Infection: A Meta-analysis

Rui Qi, Yu-ting Huang, Jian-wei Liu, Yue Sun, Xi-feng Sun, Hui-Ju Han, Xiang-Rong Qin, Min Zhao, Li-jun Wang, Wenqian Li, Jun-hong Li, Cong Chen, Xue-jie Yu

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O U T L I N E

1. Introduction

1.1 Human noroviruses

1.2 Asymptomatic norovirus infections

1.3 Studies about asymptomatic norovirus infections

2. Methods

2.1 Literature search

2.2 Study selection

2.3 Data extraction and analysis

3. Results

3.1 Prevalence of asymptomatic norovirus infection

3.2 Additional findings

4. Discussion

4.1 Global prevalence of asymptomatic norovirus infection

4.2 Outstanding questions

4.3 Interpretation

4.4 Conclusion

5. Limitations

6. Conclusion

7. Acknowledgments

8. References

9. Appendix

10. Supplementary materials

1. Introduction

Human noroviruses (NoVs) are the most common cause of acute gastroenteritis and are responsible for substantial morbidity and mortality worldwide [1,2]. NoV is responsible for 19–21 million illnesses, 1.7–1.9 million outpatient visits, 400,000 emergency department visits, 56,000–71,000 hospitalizations, and 570–800 deaths annually in the United States alone [3].

Studies about asymptomatic norovirus infections have been frequently reported. However, the mechanism of how NoV results in asymptomatic or symptomatic infection is unclear. The possible reasons for presence of asymptomatic infection may include long-term shedding from a previous symptomatic episode and truly asymptomatic infection due to lack of susceptible factors to symptomatic infection. However, human challenge studies [4] have showed the appearance of truly asymptomatic infection rather than long-term shedding from a previous symptomatic episode. Understanding the prevalence of asymptomatic NoV infection could be important for further studies. Less attention is usually paid to asymptomatic individuals and their environmental contaminants which may facilitate the transmission of norovirus. The understanding of asymptomatic and symptomatic infection would be useful in successfully presenting and applying public health control policy. In 2011, we conducted a study for NoV detection among asymptomatic children from kindergartens and primary schools in Changzhou City, China. The proportion of asymptomatic NoV infection was about 4% [5]. In an Australian research, NoV was not detected in 399 asymptomatic people [6]. In addition, more than 30% of samples from asymptomatic children in South Africa were determined to be NoV positive. The prevalence of asymptomatic NoV infection varied in different studies. In view of this, we aimed to summarize the overall prevalence of asymptomatic NoV infection. We assessed the prevalence by subgroup variables (study designs, geographic groups, objects and
2. Methods

2.1. Search Strategy and Selection Criteria

We designed two strategies for searching records. First, we identified publications containing the proportion of asymptomatic NoV infections published before October 15, 2017 in PubMed, Ovid, Scopus and Web of Science. According to different search characters in these search engines, different search terms were used. The keywords included: “norovirus”*, “Norwalk”, “asymptom*”, “gastroenter*”, “calicivirus”, “enteric*”, “entero*”. During the stage of full-text screening, relevant references cited by those articles were reviewed for selection. Our principal summary data were the total number of asymptomatic samples together with the positive number or positive rate. The prevalence of asymptomatic NoV infections varied in different studies and ranged from 0 to more than 30%. Some factors had an impact on prevalence, for example, geographic regions.

2.2. Data Extraction

Our principal summary data were the total number of asymptomatic samples together with the positive number or positive rate. The following data were extracted if provided from articles: author, year of publication, country, total number, positive number, positive rate, study design, setting, object, age, specimen, definition of “asymptomatic”, study date, and method used for detection.

Asymptomatic samples were designed to be collected from healthy participants in a cross-sectional study, the control group of a case–control study, or healthy follow-up participants in a cohort study. Therefore, we stratified study designs into three groups. Settings were also stratified into three groups (community, hospital, or other). Age was not grouped because its range varied among these studies. Instead of age-stratum, we stratified a group containing children and adults by objects of studies. “Asymptomatic” is considered if a person is a carrier for a disease or infection but experiences no symptoms. There was no consensus among the studies on this definition. Some studies defined “asymptomatic” as healthy persons with no symptoms of gastroenteritis (diarrhea, vomiting, or fever, etc.). Others included people without symptoms of gastroenteritis for at least 1 week prior and more than 3 weeks after the day of stool collection. Finally, in some studies, norovirus was detected in nondiarrheal stool specimens collected from healthy persons, but it was unknown if they had vomiting or other symptoms. We grouped the studies into two categories of asymptomatic: (1) those with either a precise definition of asymptomatic or which did not fulfill a clear symptomatic definition and (2) those without diarrhea. Some studies were conducted in different settings and data were extracted individually.

2.3. Statistical Analysis

We used Q-test to provide a test of significance for heterogeneity. Meta-regression was used to examine the impact of subgroup variables on heterogeneity. R²-adjust was the percentage of heterogeneity accounted for by the addition of variables into the Meta-regression model as compared to an “empty” model. In other words, it was the percentage of the heterogeneity explained by the subgroup variables. Random-effect models were fitted to generate estimates of overall and subgroups prevalence using the inverse-variance method. To have better statistical properties, the raw proportions were first log-transformed in order to be closer to a normal distribution and whose sampling variance can be better approximated. When the number of NoV positive samples was equal to 0, a value of 1/2 was added for calculation [7]. The test statistics of the individual coefficients in meta-regression models were based on methods of R metao packages [7]. An omnibus test of all the model coefficients is conducted that excludes the intercept. The omnibus test is based on a chi-square distribution with m degrees of freedom (m being the number of coefficients tested). The Knapp and Hartung method [8] is an adjustment to the standard errors of the estimated coefficients, which helps to account for the uncertainty in the estimate of the amount of heterogeneity and leads to different reference distributions. Individual coefficients and confidence intervals are then based on the t-distribution with k-p degrees of freedom, while the omnibus test statistic then uses an F-distribution with m and k-p degrees of freedom (p being the total number of model
coefficients). All analysis and plots were run with R software and the \textit{metafor} package and \textit{rworldmap} package (for world map) [7,9].

2.4. Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

853 studies were identified through initial searching. Of these, 466 were then reviewed by their titles and abstracts, and 329 were excluded. We assessed the remaining 137 full-text articles for eligibility, and 57 of them were excluded because they did not fulfill inclusion criteria such as lacking pertinent information or were conducted for other aims. Twenty six references were added while reviewing those 137 full-text articles with the selection criterion being cited by articles to show prevalence of asymptomatic infection. One of these 26
refeferences was included and the other 25 references either had been included in previous selections or did not meet the inclusion criteria. Finally, 81 studies were included for analysis (Fig. 1), and of these, 15 were under outbreaks circumstances while 71 were not. Because 5 studies reported more than one result, the number of stratum-specific studies for analysis did not sum up to the overall number.

Asymptomatic individuals mainly were from: (1) cross-sectional studies, (2) case–control studies control group, and (3) cohort studies. The numbers of studies with these three designs were 33, 21, and 17, respectively. Studies were selected from 36 countries (Fig. 2). More studies were from China (9), Brazil (7), United States (6), South Korea and Japan (5) than from other countries such as Australia and New

**Table: Country Comparison**

| Study         | Country         | Total N | Prevalence |
|---------------|-----------------|---------|------------|
| Marshall,2004 | Australia       | 399     | 0.00       |
| Subedi,2004  | Nepal           | 102     | 0.00       |
| Nataraaju,2010 | India          | 312     | 0.01       |
| Kaarmie,2016 | Sweden          | 436     | 0.01       |
| Verraccchio,2006 | United States | 484     | 0.01       |
| Aragao,2013  | Brazil          | 57      | 0.01       |
| Jesing,2013  | South Korea     | 624     | 0.01       |
| de Wit,2001 | Netherlands     | 574     | 0.01       |
| Braun,2012   | United States   | 78      | 0.01       |
| Zhiang,2017  | United States   | 150     | 0.01       |
| Olesen,2005 | Denmark         | 629     | 0.01       |
| Vicentini,2013 | Italy          | 264     | 0.01       |
| Saab,2016    | Spain           | 49      | 0.01       |
| Koo,2016     | Vietnam         | 217     | 0.01       |
| Zhirakovskaia,2015 | Russia  | 219     | 0.02       |
| Utsumi,2017 | Indonesia       | 512     | 0.03       |
| Tra My,2018 | Vietnam         | 608     | 0.04       |
| Zhirakovskaia,2015 | Russia  | 142     | 0.03       |
| Cheon,2011  | South Korea     | 208     | 0.03       |
| Yu,2011     | South Korea     | 776     | 0.03       |
| Karsten,2009 | Germany         | 522     | 0.03       |
| Zhang,2016  | China           | 170     | 0.04       |
| Paschke,2011 | Germany         | 56      | 0.04       |
| Pokorn,2017 | Slovenia        | 150     | 0.04       |
| Monica,2007 | India           | 173     | 0.04       |
| Qi,2015     | China           | 511     | 0.04       |
| Melamed,2017 | United States  | 178     | 0.04       |
| Chang,2017  | China           | 680     | 0.05       |
| Parashar,2004 | Peru           | 248     | 0.05       |
| de Wit,2001 | Netherlands     | 669     | 0.05       |
| Cheon,2011  | South Korea     | 200     | 0.05       |
| Akhara,2005 | Japan           | 633     | 0.06       |
| Costantini,2016 | United States | 18     | 0.06       |
| Quevedt,2016 | Burkin Faso     | 500     | 0.06       |
| Cardemil,2017 | Nepal          | 358     | 0.06       |
| Yasven,2012 | Ethiopia        | 57      | 0.07       |
| Tang,2013   | China           | 98      | 0.07       |
| Kruikamp,2015 | Ghana          | 651     | 0.07       |
| Farkas,2000 | Mexico          | 66      | 0.07       |
| Mendratha,2014 | Brazil        | 539     | 0.08       |
| Yee,2009    | Peru            | 76      | 0.08       |
| O’Ryan,2009 | Chile           | 2278    | 0.08       |
| Moyo,2014   | Tanzania        | 249     | 0.09       |
| Porcaccaring,2009 | Tanzania    | 312     | 0.09       |
| Moyo,2014   | Tanzania        | 312     | 0.09       |
| Ensinkink,2014 | Netherlands  | 49958   | 0.10       |
| Gastanaduy,2015 | Ecuador        | 146     | 0.10       |
| Frange,2015 | France          | 43      | 0.12       |
| Bucardo,2010 | Nicaragua       | 165     | 0.12       |
| Trainor,2013 | Malawi          | 505     | 0.12       |
| Bucardo,2017 | Nicaragua       | 261     | 0.12       |
| Okayashi,2008 | Japan          | 159     | 0.13       |
| Becker–Dreys,2014 | Nicaragua | 106     | 0.13       |
| Salti,2014  | Peru            | 3660    | 0.14       |
| Goncalves,2010 | Brazil        | 90      | 0.13       |
| Dabilla,2017 | Brazil          | 123     | 0.13       |
| Menon,2010  | India           | 148     | 0.14       |
| Anmar,2007  | United Kingdom  | 2205    | 0.14       |
| Lopman,2015 | United States   | 1016    | 0.14       |
| Horwood,2017 | Papua New Guinea | 148    | 0.14       |
| Rouhani,2016 | 8 COUNTRIES    | 2307    | 0.14       |
| Siqueira,2017 | Brazil        | 124     | 0.20       |
| Grant,2017  | United States   | 343     | 0.20       |
| Giadalone,2008 | Italy          | 26      | 0.21       |
| Huynen,2013 | Burkin Faso     | 125     | 0.25       |
| Ayubekong,2011 | Cameroon    | 54      | 0.30       |
| Garcia,2006 | Mexico          | 181     | 0.30       |
| Matison,2010 | Botswana       | 28      | 0.31       |
| Zhang,2011  | China           | 53      | 0.36       |
| Kabul,2016  | South Africa    | 50      | 0.36       |
| Castro,2006 | Brazil          | 55      | 0.36       |

**Fig. 3.** Forest plot showing the results of 71 studies estimating prevalence of norovirus asymptomatic infection ($\tau^2 = 0.60, P < 0.01$ test for heterogeneity). The figure showed prevalence with 95% confidence intervals in the individual studies based on a random-effects model with studies ordered by prevalence. A line was used to represent the confidence interval of estimate. The prevalence estimated was marked with a solid black square. The size of the square represented the weight that the corresponding study exerted in the meta-analysis. The size of the square and the length of confidence interval corresponded to the size of the study and therefore the precision of the estimate. The pooled prevalence was marked with a filled polygon that had a dotted line from its upper point. Confidence intervals of pooled estimates were displayed as the width of the polygon. N was the number of NoV positive samples, value of 1/2 was added to N for calculation when N was equal to 0.
Zealand, both of which had only 1 study included. One study conducted in eight countries was not stratified data by countries due to incomplete information, and instead it was reviewed as a whole study. The number of communities (30) and hospitals (26) where studies were conducted was similar. Subjects of most studies were children (56), and only eight articles studied prevalence of adults, with five of eight focused on food handlers. Most of these studies had a definition of “asymptomatic” (or not fulfilling a defined case definition), while nineteen studies only included individuals who were without diarrhea as research objects. “Asymptomatic” was referred to but not defined in eleven studies. Among studies which had information about genotypes, about 80% (922/1157) of asymptomatic individuals were GI and 20% (235/1157) were GII.

Of 71 studies, asymptomatic NoV prevalence was estimated by random-effect model at 7% (95% CI: 6%–9%, $\tau^2 = 0.60$, $P < 0.01$ test for heterogeneity) (Fig. 3). The sources of heterogeneity may be due to many factors such as study design, population, etc. Results of meta-regressions showed that heterogeneity was 7.53%, 8.16%, 18.10%, 17.41% and 11.13%, respectively for 5 subgroups variables (designs, environment, objects, geographic regions, and definition of “asymptomatic”). By design, prevalence from the control group (7%) in case–control studies was similar with that from cross-sectional studies (5%) (95% CI: 6%–9%, $\tau^2 = 0.60$, $P < 0.01$ test for heterogeneity) (Fig. 3). By geographic regions, Africa, Meso America and South America had higher prevalence (15%, 14%, 11%, respectively) while the prevalence in Europe and North America was lower (4%). By environmental settings, prevalence was about 8% in both the community and hospital ($P = 0.66$). Prevalence was higher in children (8%) than adults (4%) ($P = 0.07$). For food handlers, prevalence was estimated at 3%, which was similar with prevalence in adults. Studies that provided a clear definition of “asymptomatic” (or not fulfilling a clear case definition) had a prevalence of 7%, which was not significantly different from prevalence of studies that only allowed individuals without diarrhea for enrollment (9%) (Results with confidence bounds were shown in Fig. 4).

In the 15 studies where asymptomatic individuals were exposed under outbreak circumstances, pooled prevalence of infection was 18% (95% CI: 10%–30%, $\tau^2 = 1.42$, $P < 0.01$ test for heterogeneity) (Fig. 5). Settings where outbreaks occurred included: care facilities, catering services, hotels, schools, hospitals, and cruise ships. Transmission pathways included: person to person, foodborne, waterborne, and environment (Data not shown).

4. Discussion

Noroviruses are commonly detected in asymptomatic individuals with possible reasons including pre/post-symptomatic long-term shedding, and true asymptomatic infection due to lack of susceptible factors to symptomatic infection. In a human challenge study [4], samples from pre-challenge and post-challenge days were tested for NoV shedding. First, this experiment resulted in the appearance of asymptomatic volunteers. Second, asymptomatic and symptomatic volunteers had a similar shedding pattern (viral load, duration of shedding). Another study of a large population for NoV shedding also indicated that shedding in asymptomatic subjects was similar to symptomatic subjects [10]. Many studies reported that NoV bound to histo-blood group antigens (HBGA), which were expressed by the fucosyltransferase 2 (FUT2) gene. Individuals with a functional FUT2 gene were termed “secretors”. A systematic review [11] of association between HBGA and susceptibility showed that secretors were about 2–10 times more likely to be infected than non-secretors. HBGA had been reported to play a role as cellular receptors for NoV attachment [1]. In this view, asymptomatic infection may not only result from pre/post-symptomatic shedding. Similar norovirus shedding patterns between symptomatic and asymptomatic individuals in conjunction with lesser attention usually paid to asymptomatic individuals may facilitate the transmission of norovirus.

**Fig. 4.** Results of pooled prevalence by subgroup. ($n =$ number of studies in this subgroup). The figure showed pooled prevalence with 95% confidence intervals in the individual subgroups based on random-effects models. Black polygon was the estimated prevalence in the individual subgroups. The width of the polygon represented confidence interval of pooled estimate. Because some studies reported different results of strata, the number of stratum-specific studies for analysis didn’t sum up to the overall number. The overall pooled estimate was added for comparison by a polygon that had a dotted line. For all subgroups, P-values of tests for heterogeneity were <0.01. The sources of heterogeneity of prevalence studies were due to many factors, significant heterogeneities of subgroups divided respectively by each factor were still existed.
In practice, estimates of prevalence of asymptomatic NoV infections are affected by study design, settings, population, the distinction between symptomatic and asymptomatic individuals and other factors. Based on the 71 studies in our analysis, prevalence of asymptomatic NoV infection was 7%. The same result was obtained in another study in which prevalence was estimated from 20 studies [12], where asymptomatic individuals were only from control groups matched with cases in case-control studies. Studies with this design also met our study inclusion criteria, and our result in this design was also 7%. Beyond that, our studies included another two designs of studies. Prevalence was higher in cohort studies, and the proportion was calculated as the sum of several specimens collected from each individual divided by total number of positive individuals. Cohort studies might be a source of heterogeneity because detection of NoV in their stool may be shedding from a previously symptomatic infection. Information on the length of follow up or interval between previous reports of symptoms and sample collection was rarely given in texts. Norovirus prevalence tended to be higher in cases of acute gastroenteritis compared with asymptomatic infection. A pooled prevalence of norovirus in 187,336 patients with acute gastroenteritis from 175 articles was as high as 18% (95% CI 17–20) [13]. The high prevalence of symptomatic and asymptomatic norovirus infection showed that this pathogen brought heavy burdens and targeted control programs were needed for norovirus prevention.

We noted the same prevalence from community and hospital. Generally, prevalence of symptomatic infections in hospitals might be regarded as higher than in the community, but for asymptomatic infection, it cannot be known as the ranges of case–matched control for inclusion were not defined clearly in the studies. A few articles enrolled control individuals who were attending outpatient for routine health checks or conditions unrelated to gastroenteritis [13]. These individuals in this kind of control group had the same characteristics as those in the community. Prevalence in children was higher, suggesting that asymptomatic infection was likely associated with immunity because children have lower resistance to illness than adults [14]. One important mode of NoV infection was via contaminated food. NoV was considered in the United States the leading known foodborne agent, accounting for over 50% of foodborne illnesses annually [15]. Foodborne transmission was significant in NoV outbreaks [16]. The estimation of food handlers’ asymptomatic infection from five studies was 3% with a 95% CI: 1–7%. Due to the lower prevalence, food handlers are not suspected to be susceptible population for asymptomatic infections. In our selected studies, there was one study which was conducted in eight countries: Bangladesh, Brazil, Pakistan, Peru, South Africa, Tanzania, Nepal, and India [17]. The conclusion about asymptomatic infection in the previous study was 19%, ranging from 2.2% in Nepal to 30.4% in South Africa. Their study population was only infants aged 0–2 years old from low- and middle-income countries, which was a possible reason for the high prevalence as children are more susceptible for NoV [14] and norovirus is spread by the fecal oral route, suggesting age and hygiene status might be factors associated with norovirus infections. Due to the lack of data stratified by countries in this study, we did not include it in subgroup analysis by geographic regions. A recent study [18] generated a pooled estimate of the prevalence of asymptomatic norovirus infection from 13 articles centered in Latin America. The prevalence they estimated was 8% (95% CI: 4–13) which was similar with our result. One cause of this small variation may be because we included more articles (14 from South America and 5 from Meso America), and that their data were collected only between 1989 and 2012.

As we hypothesized, asymptomatic prevalence (18%) was much higher in the context of outbreaks than in healthy individuals not known to be in contact with other infected symptomatic people. More data with outbreak of norovirus would be needed in the future for better analysis.

Our study has some limitations. First, older adults were vulnerable to gastroenteritis [19], but there were not enough articles available for inclusion to have a stratified analysis for elderly people. Age, an important factor to NoV, could not be grouped into categories as ranges in studies were highly varied, even though we tried different ways. Other possible factors which could have an impact on prevalence were not considered, for example, seasonality. A few studies reported different prevalence of asymptomatic NoV infection by seasons [20,21]. Many of our studies involved an extended span of time making it difficult to distinguishably estimate the pattern of seasonality. In addition, we calculated the proportion of genotypes of asymptomatic NoV cases from articles having this information. About 80% (922/1157) were GII and 20% (235/1157) were GI. From theses proportions, we could not say that GII was the major genotype associated with asymptomatic infection as determining the association between genotypes and asymptomatic cases requires minimum proportion of genotypes of symptomatic NoV cases. Although 80% of infections were GII in asymptomatic cases, symptomatic human

| Study          | Country          | Total N | Prevalence |
|----------------|------------------|---------|------------|
| Zheng, 2015   | China            | 268     | 13.05%     |
| Thornley, 2013| New Zealand      | 8       | 0.06%      |
| Kimura, 2011  | Japan            | 85      | 6.07%      |
| * Ozawa, 2007 | Japan            | 1845    | 1330.07%   |
| Iizuka, 2010  | Japan            | 11      | 1.09%      |
| * Costantini, 2016 | United States | 34      | 4.12%      |
| Lai, 2013     | China            | 23      | 3.03%      |
| Yang, 2010    | United States    | 249     | 40.16%     |
| He, 2016      | China            | 86      | 14.16%     |
| Xue, 2014     | China            | 50      | 9.18%      |
| Gallimore, 2004| United Kingdom  | 99      | 24.02%     |
| Hoebe, 2004   | Netherlands      | 16      | 6.03%      |
| Wang, 2016    | China            | 31      | 15.08%     |
| Medici, 2009  | Italy            | 8       | 4.50%      |
| * Sabri, 2016 | Spain            | 188     | 1010.54%   |

**Fig. 5.** The same as in Fig. 3, but for prevalence of norovirus asymptomatic infection under outbreaks circumstance ($\chi^2 = 1.42, P < 0.01$ test for heterogeneity) from 15 studies. The length of confidence interval corresponded to the sample size of the study and therefore the precision of the estimate. *, Studies with prevalence were calculated in N outbreaks (N > 1).
norovirus infections were also caused mostly by GII. More evidences are needed to explore the associations between genotype and asymptomatic cases. Finally, Q test for heterogeneity in models was highly significant, suggesting that other factors that were not considered might have had remarkable effects on asymptomatic prevalence.

In conclusion, the prevalence of asymptomatic NoV infection estimated through meta-analysis is 7% and varies depending on different countries, settings and objects of study. The prevalence in context of outbreak exposure is as high as 18%. The high prevalence indicated asymptomatic individuals must not be overlooked. Asymptomatic individuals may play an important role in NoV transmission. This knowledge could have an impact on the development of transmission prevention strategies. More work will be needed to better understand and interpret the presence of asymptomatic infection and the roles it plays in NoV transmission.

Contributors

QR and HYT designed the study, did the literature search, data extraction, analyzed data and interpreted data. QR drafted the manuscript. YXJ designed the study, interpreted data, edited the manuscript and contributed to the manuscript. LJW, HHJ, SXF, QXR and LWQ helped do the literature screen and data extraction. SY, ZHM and WLJ helped contribute to the manuscript. LJW, HHJ, SXF, QXR and LWQ helped YXJ designed the study, interpreted data, edited the manuscript and contributed to the manuscript. LJW, HHJ, SXF, QXR and LWQ helped update articles published in 2017. LJH and CC helped with R program.

Declaration of Interests

We declare no competing interests.

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Appendix A

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