

A systematic review and meta-analysis of the prevalence of norovirus in cases of gastroenteritis in developing countries

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Abstract

Background: While norovirus (NoV) is well known as a leading causal pathogen for acute gastroenteritis in developed countries, structured data on prevalence in developing countries are not available thus far. This review aims to estimate the prevalence of NoV in cases of gastroenteritis in developing countries based on recently published reports.

Methods: Relevant studies were identified by searching PubMed and Web of Science for the period January 1, 1990 through March 31, 2016. We included studies performed in developing countries with a study period of at least 12 months and which provided information on polymerase chain reaction (PCR)-confirmed NoV prevalence in patients diagnosed with acute gastroenteritis. A metaanalysis was conducted on NoV prevalence, focused on viral genogroups GI and GII, in cases of acute gastroenteritis.

Results: Using evidence from 178 articles, the estimated NoV prevalence among 148,867 patients with acute gastroenteritis was 17% (95% confidence interval [CI]: 15–18%). The prevalence decreased from 18% (95% CI: 16–20%) for upper middle-income countries to 15% (13–18%) and 6% (3–10%) for lower middle- and low-income countries, respectively. There were no significant differences in NoV prevalence by age group (under 5 years, 5 years and over, and mixed ages) or severity of symptoms as defined by community, outpatient, or inpatient setting. The pooled prevalence of NoV GII (15%, 95% CI: 13–17%) was significantly higher than that of NoV GI (1%, 95% CI: 1–1%) in patients with acute gastroenteritis.

Conclusion: From the evidence considered in this review, the estimated prevalence of NoV in patients with acute gastroenteritis in developing countries was 17%. This estimate can be used to evaluate the burden of NoV-associated acute gastroenteritis in developing countries, which is currently unclear due to poor diagnosis and surveillance systems, and the estimation may enhance the development of human NoV vaccines.

Abbreviations: 95% CI = 95% confidence intervals, NoV = norovirus, PCR = polymerase chain reaction.

Keywords: developing country, diarrhea, gastroenteritis, meta-analysis, prevalence norovirus

1. Introduction

Acute gastroenteritis contributes significantly to the burden of disease worldwide. A previous study^[1] indicated that 801,000

worldwide mortalities in children under 5 years of age are associated with diarrheal disease. The incidence and mortality rates of diarrhea are much higher in low-income than in middle- and high-income countries.^[2]

Norovirus (NoV) is an important cause of nonbacterial gastroenteritis worldwide.^[3,4] According to Ahmed et al,^[5] global NoV prevalence in community cases of gastroenteritis was 24%, while the prevalence in outpatients and patients admitted to hospitals for treatment of symptoms associated with NoV were 20% and 17%, respectively. NoV has surpassed rotavirus as the predominant cause of acute gastroenteritis in children in countries where rotavirus vaccination has been introduced.^[6,7] Although 7 genogroups of NoV (GI–GVII) have been identified,^[8] 2 genogroups (GI and GII) are the main causes of NoV-associated gastroenteritis; a recent increase in NoV GII-associated gastroenteritis was reported not only in developed countries^[9–13] but also in developing countries.^[14,15]

There is a considerable difference in access to safe water, sanitation, and hygiene between developed and developing countries,^[16,17] which may correlate with a higher risk of NoV-associated gastroenteritis in developing countries. Patel et al^[3] estimated that NoV in cases of gastroenteritis in developing countries was 12% among children under 5 years old. However, this estimation was based on datasets from 11 studies in only 7 developing countries; the prevalence varies by country depending on location, age group, economic status, severity of symptoms,

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and epidemic conditions. Considering these factors, Ahmed et al.^[5] performed a meta-analysis of the prevalence of NoV in cases of gastroenteritis on a global scale but mentioned that a clear data gap remains for determining the NoV prevalence in developing countries due to lack of high quality reports on the prevalence in these countries. We searched the relevant reports from developing countries defined by World Bank as low-income and middle-income countries,^[18] using the databases other than those used by Ahmed et al.,^[5] including the most recent publications. Using the large number of papers identified, this study aimed to estimate the prevalence of NoV in cases of acute gastroenteritis in developing countries from 1990 to 2016 by means of systematic review and meta-analysis.

2. Methods

2.1. Search strategy and selection criteria

The procedure to search and select studies relevant to this review was similar to Ahmed et al.^[5] A systematic search was performed using PubMed and Web of Science databases of studies published between January 1, 1990 and March 31, 2016. The search terms used were as follows: “Noroviruses,” “Norwalk-like Viruses,” “Norwalk like Viruses,” “Small Round-Structured Viruses,” “Round-Structured Viruses, Small,” and “Small Round Structured Viruses.” Full-text articles were assessed and selected if they met the following inclusion criteria: used PCR-based diagnostics for all stool specimens from patients, enrolled patients who presented with symptoms of acute gastroenteritis, were performed in developing countries as defined by the World Bank,^[18] and had a study period of at least 12 months.

We excluded papers which did not have an English abstract, did not show the number of patients with acute gastroenteritis or patients positive for NoV, or percentages that could be used for calculating prevalence. If the same data were repeated in multiple studies, only the most complete study was considered. Additionally, papers, which reported neither diarrhea nor vomiting as common symptoms of gastroenteritis, were also excluded.

2.2. Data extraction

From the eligible articles, we obtained the following information: first author, title, journal, year of publication, country, period and duration of study, surveillance setting, number of patients with acute gastroenteritis, number of patients positive for NoV, number of patients without acute gastroenteritis, number of cases tested without acute gastroenteritis but positive for NoV (asymptomatic NoV infection), and age group. Data were stratified by age of subjects, surveillance setting, and country income level categorized according to World Bank classifications.^[18] For age, the data were stratified into 2 groups: under 5 years, and 5 years and over. The data unable to be stratified in this manner were not stratified and treated as “mixed age”. For surveillance setting, the data were stratified into 4 different settings as a proxy for severity of symptoms: “community” indicating patients with relatively mild symptoms which were only recognized by community cohort studies, “outpatients,” “inpatients” including those who visited an emergency department, and “other setting,” which included studies that contained no specific setting or unstratified data. For income level, data were stratified based on estimates of gross national income (GNI) per capita for 2014 countries were classified into high income, upper middle-income, lower middle-income, or low-income groups.^[18] In addition, where possible, the data were stratified

by NoV genogroups as well. Studies performed during December 1, 2002 to January 31, 2003 or December 1, 2006, to January 31, 2007 were considered as reporting pandemic data, while the remaining studies were considered as reporting endemic data according to the definition of a previous review.^[5]

2.3. Statistical analysis

A meta-analysis was conducted for NoV prevalence in cases of acute gastroenteritis for prevalence of NoV GI and GII and asymptomatic NoV infection. Heterogeneity between studies was evaluated using the I^2 test. All analyses were performed using STATA software version 14 (Stata Corp, College Station, TX).^[19] P -values $<.05$ were considered statistically significant.

3. Results

A literature search of 2 electronic databases identified 8280 relevant articles for the present systematic review (Fig. 1). We narrowed down the relevant articles through assessment of titles and abstracts and reviewed 539 full-text articles for eligibility; 377 articles were excluded based on exclusion criteria (83 were from high-income countries, 74 were outbreak reports, 11 were written in foreign language, 19 discussed laboratory methods, 11 did not use PCR-based diagnosis, 8 were laboratory reports, 17 included insufficient data, 3 reported traveler’s diarrhea, 69 had a study period <1 year, 37 reported no data, and 45 were unable to be assessed). A total of 162 papers met the inclusion criteria, which included 85 studies from Ahmed et al.,^[5] and full data were extracted from all included studies. The final dataset consisted of 178 papers from 46 countries; a majority of studies were from China ($n=57$), Brazil ($n=22$), India ($n=18$), and Thailand ($n=17$) (Fig. 2). Study countries were categorized into upper middle- ($n=19$), lower middle- ($n=21$), and low-income countries ($n=6$) (Table 1). The number of articles (178) is relatively low for a time period of >25 years. This is probably because NoV usually causes a relatively mild gastroenteritis with a short duration, resulting in a low mortality, and it may have not received much attention in those developing countries.

A pooled analysis of all 178 articles revealed the NoV prevalence among 148,867 patients with acute gastroenteritis was 17% (95% CI: 15–18; $P <.01$ test for heterogeneity [P_b]) as shown in Table 2. There were no differences in NoV prevalence among the 3 age groups assessed ($P_b=0.727$). Country income level significantly affected the NoV prevalence; a decrease from 18% in upper middle- to 15% in lower middle- and 6% in low-income countries ($P_b <0.001$) was noted. Prevalence during pandemics was significantly different from that under endemic time periods ($P_b <0.001$). There were no significant differences in prevalence characterized by severity of symptoms defined by community (16%), inpatient (17%), or outpatient settings (16%) ($P_b=0.897$). Related to the severity, NoV prevalence was noted in 5% of patients without gastroenteritis (95% CI: 4–8%; $I^2=95.25\%$; $P_b <0.001$) (Table 3).

The pooled analysis revealed a higher prevalence of NoV GII (15%; $I^2=98.57\%$, $P <.001$) than NoV GI (1%; $I^2=92.91\%$, $P <.001$) in patients with acute gastroenteritis, as shown in Tables 4 and 5. The prevalence of NoV GII, which was the predominant genogroup, in patients with acute gastroenteritis was assessed by country income, pandemic or endemic classification, and setting as an indicator of symptom severity. NoV GII prevalence was lower in studies only during pandemic periods (13%, 10–15) than in whole studies including endemic

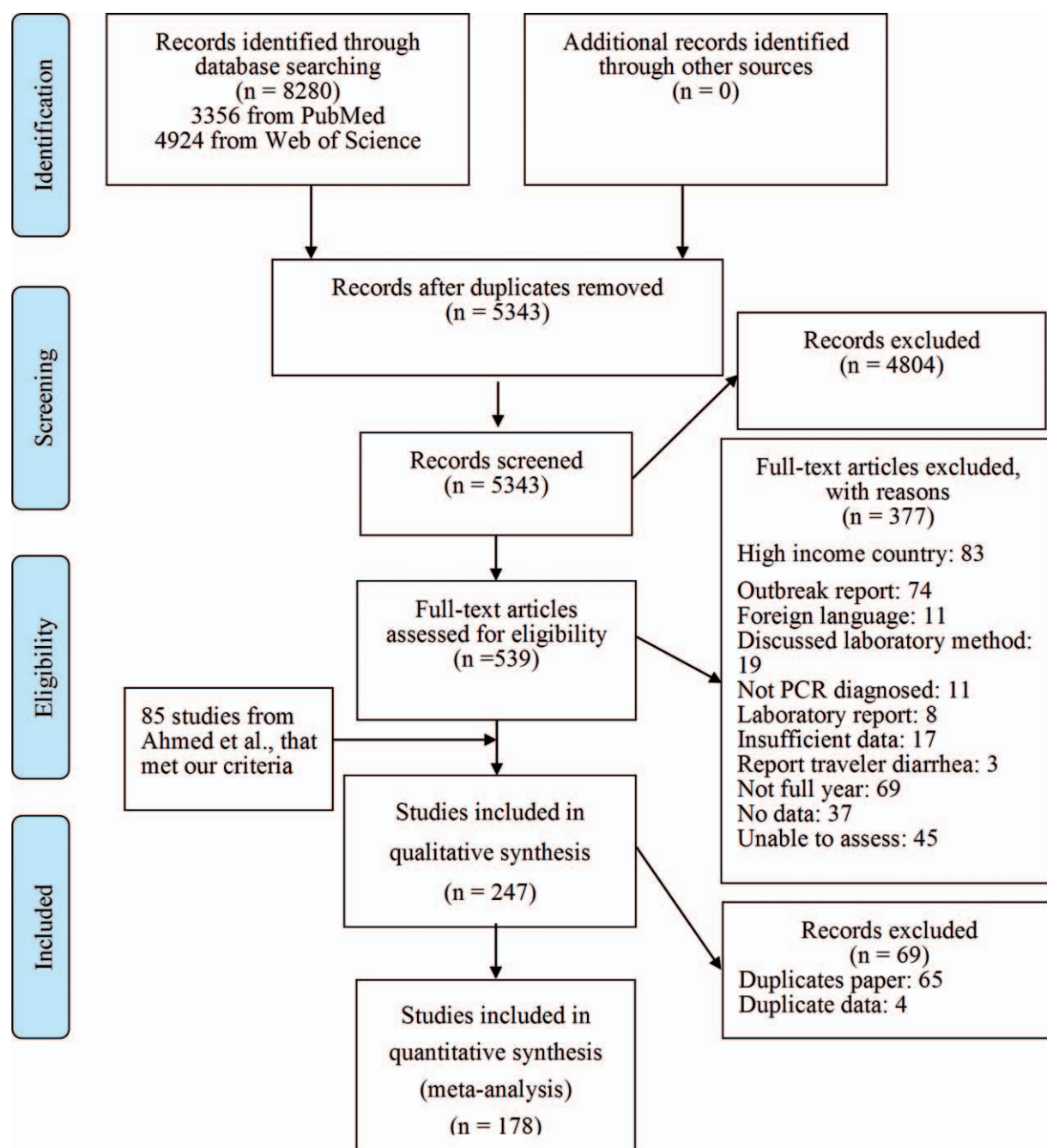


Figure 1. Study profile.

periods (17%; 14–19; $P_b < 0.01$). The NoV GII prevalence was higher in upper middle-income countries (16%; 14–19; $P_b < 0.001$) than lower middle- (14%; 11–18; $P_b < 0.001$) or low-income countries (6%; 3–11; $P_b < 0.001$). There were no differences in the NoV GII prevalence ($P_b = 0.557$) by study setting (as an indicator of symptom severity).

4. Discussion

NoV is recognized as an important cause of nonbacterial gastroenteritis worldwide. Although acute gastroenteritis may occur more frequently in developing countries due to poor sanitation and hygiene, NoV prevalence is still unknown due to a

lack of published well-structured data. Our meta-analysis indicates that the NoV prevalence in cases of acute gastroenteritis in developing countries was 17%.

Our review used a similar design for the systematic review as Ahmed et al,^[5] with small modifications. For example, we stratified economic status based on the country income level^[18] instead of World Health Organization (WHO) mortality stratum^[20] in order to highlight differences among developing countries. We also added an additional analysis of the data stratified by NoV genogroup.

NoV prevalence in this study was similar to that in Ahmed et al.^[5] They estimated the global prevalence of NoV in cases of gastroenteritis to be 18% (95% CI: 17–20%) with a clearly remaining gap in developing countries. Our finding, thus, was not

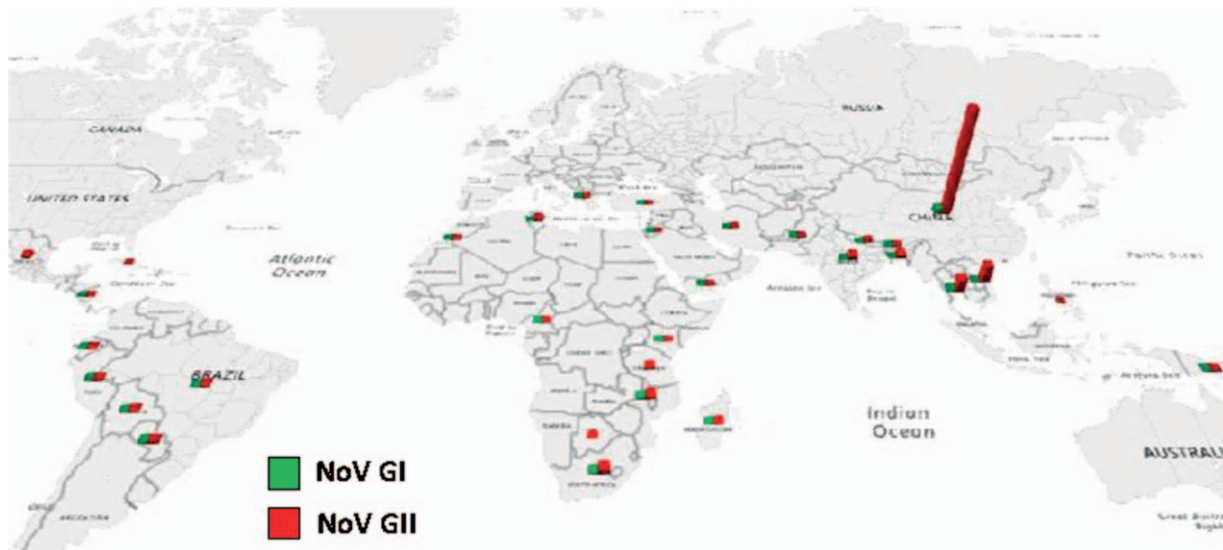


Figure 2. Countries reported on NoV GI and GII prevalence in meta-analysis. NoV=norovirus.

consistent with the previous reports that the prevalence of NoV in case of gastroenteritis in developing countries should be higher than in developed countries due to limited access to safe water, sanitation, and hygiene.^[16,17] Poor surveillance about NoV and the tendency of people not to use medical services for mild diseases such as gastroenteritis caused by NoV could cause the underestimation of the prevalence in developing countries. Even in this situation, we found much higher estimates of NoV prevalence than those reported in Africa (11%)^[21] and Latin America (15%),^[22] indicating that the other regions targeted in the present study (i.e., Asia and the Middle East) probably have a higher prevalence.

The present study also revealed a significant difference in NoV prevalence based on genogroups GI (1%) and GII (15%). The much higher prevalence estimate of NoV GII is supported by many previous studies^[21–24] which show that 37% to 100% of NoV-associated acute gastroenteritis is associated with this genogroup.

Table 1
Distribution of data among various strata.

	Number of studies (n=178)	Cases tested (n=148,867)
Age groups		
<5 y	114	87,684
≥5 y	22	7545
Mixed	72	53,638
Setting		
Inpatient	118	69,290
Outpatient	43	58,312
Community	15	5025
Other	32	16,240
Country income level		
Low income	6	14,577
Lower middle income	21	31,232
Upper middle income	19	103,058
Pandemic period		
Included	54	34,473
Not included	154	114,394

By age, prevalence was similar in patients with acute gastroenteritis under 5 years (16%; 14–18%), 5 years and over (17%; 13–21%), and of mixed ages (17%; 14–21%). Our finding was consistent with Ahmed et al,^[5] who pointed out that global NoV prevalence in under 5 years, 5 years and over, and mixed ages was similar (18% [95% CI: 15–20%], 18% [95% CI: 13–24%], and 19% [95% CI: 17–21%], respectively).

By country income, prevalence decreased as income decreased. Since low-income countries have more pathogens to cause acute gastroenteritis than other countries, the proportion of NoV causing acute gastroenteritis in these countries was lower than countries of other income statuses.^[5] Another possible reason for this trend is that people in low-income countries tend not to use

Table 2
NoV prevalence in patients with gastroenteritis.

	I ² (%)	P	Effect size (95% CI)
Age group			
<5 y	97.73	<.01	0.16 (0.14–0.18)
≥5 y	95.26	<.01	0.17 (0.13–0.21)
Mixed	98.84	<.01	0.17 (0.14–0.21)
Heterogeneity between groups			.727
Setting			
Inpatient	98.40	<.01	0.17 (0.14–0.19)
Outpatient	98.46	<.01	0.16 (0.14–0.19)
Community	95.74	<.01	0.16 (0.11–0.21)
Other	97.96	<.01	0.18 (0.14–0.22)
Heterogeneity between groups			.897
Country income level			
Low income	98.01	<.01	0.06 (0.03–0.10)
Lower middle income	97.61	<.01	0.15 (0.13–0.18)
Upper middle income	98.30	<.01	0.18 (0.16–0.20)
Heterogeneity between groups			<.01
Data in pandemic period			
Included	97.65	<.01	0.17 (0.14–0.20)
Not included	98.29	<.01	0.17 (0.15–0.18)
Heterogeneity between groups			<.001
Overall	98.27	<.01	0.17 (0.15–0.18)

CI=confidence interval; NoV=norovirus.

Table 3
NoV prevalence in patients without gastroenteritis.

	<i>I</i> ² (%)	<i>P</i>	Effect size (95% CI)
Age group			
<5 y	92.04	<.01	0.06 (0.04–0.08)
≥5 y	99.58	<.01	0.04 (0.02–0.06)
Mixed	98.02	<.01	0.05 (0.01–0.13)
Heterogeneity between groups		.411	
Setting			
Inpatient	94.67	<.01	0.06 (0.03–0.10)
Outpatient	90.86	<.01	0.04 (0.02–0.07)
Community	93.44	<.01	0.07 (0.02–0.14)
Heterogeneity between groups		.161	
Country income level			
Lower middle income	92.13	<.01	0.04 (0.02–0.07)
Upper middle income	96.98	<.01	0.08 (0.04–0.12)
Heterogeneity between groups		<.001	
Data in pandemic period			
Included	82.72	<.01	0.10 (0.05–0.17)
Not included	95.75	<.01	0.05 (0.03–0.07)
Heterogeneity between groups		.036	
Overall	95.25	<.01	0.05 (0.04–0.08)

CI=confidence interval; NoV=norovirus.

medical services for mild gastroenteritis caused by NoV because of the economic burden. This could lead to underestimation of NoV prevalence in those countries, especially in outpatient and inpatient settings.

Prevalence was similar between studies from pandemic time periods (17%; 14–20%) and studies from endemic time periods (17%; 15–18%). Our finding was consistent with Ahmed et al,^[5] which estimated the prevalence in pandemic time periods (2002–2003 and 2006–2007) and the whole periods including endemic time was 19% (95% CI: 16–22%) and 18% (95% CI: 16–20%), respectively.

By setting, prevalence was similar between patients with acute gastroenteritis in community (16%; 11–21%), inpatient settings

Table 4
NoV GI prevalence in patients with acute gastroenteritis.

	<i>I</i> ² (%)	<i>P</i>	Effect size (95% CI)
Age group			
<5 y	90.72	<.01	0.01 (0.00–0.01)
≥5 y	89.74	<.01	0.02 (0.01–0.04)
Mixed	94.94	<.01	0.01 (0.01–0.02)
Heterogeneity between groups		.041	
Setting			
Inpatient	92.5	<.01	0.01 (0.01–0.01)
Outpatient	82.92	<.01	0.00 (0.00–0.01)
Community	95.00	<.01	0.03 (0.00–0.08)
Other	94.46	<.01	0.02 (0.01–0.04)
Heterogeneity between groups		.003	
Country income level			
Low income	91.1	<.01	0.00 (0.00–0.01)
Lower middle income	91.00	<.01	0.01 (0.00–0.01)
Upper middle income	90.91	<.01	0.01 (0.01–0.01)
Heterogeneity between groups		.097	
Data in pandemic period			
Included	93.34	<.01	0.01 (0.00–0.02)
Not included	92.79	<.01	0.01 (0.01–0.01)
Heterogeneity between groups		.674	
Overall	92.91	<.01	0.01 (0.01–0.01)

CI=confidence interval; NoV=norovirus.

Table 5
NoV GII prevalence in patients with acute gastroenteritis.

	<i>I</i> ² (%)	<i>P</i>	Effect size (95% CI)
Age group			
<5 y	98.05	<.01	0.15 (0.12–0.17)
≥5 y	95.36	<.01	0.15 (0.10–0.19)
Mixed	98.98	<.01	0.16 (0.13–0.21)
Heterogeneity between groups		.704	
Setting			
Inpatient	98.78	<.01	0.15 (0.12–0.18)
Outpatient	98.73	<.01	0.17 (0.13–0.21)
Community	87.13	<.01	0.13 (0.09–0.18)
Other	96.35	<.01	0.17 (0.13–0.21)
Heterogeneity between groups		.557	
Country income level			
Lower income	98.53	<.01	0.06 (0.03–0.11)
Lower middle income	97.88	<.01	0.14 (0.11–0.18)
Upper middle income	98.38	<.01	0.16 (0.14–0.19)
Heterogeneity between groups		.001	
Data in pandemic period			
Included	97.58	<.01	0.13 (0.10–0.15)
Not included	98.50	<.01	0.17 (0.14–0.19)
Heterogeneity between groups		<.01	
Overall	98.57	<.01	0.15 (0.13–0.17)

CI=confidence interval; NoV=norovirus.

(17%; 14–19%), and outpatient settings (16%; 14–19%). Our results contradict that of previous studies. Ahmed et al^[5] estimated that global NoV prevalence was lower in community settings compared with outpatient and inpatient settings. A possible reason for the difference between our finding and the previous finding is that we stratified country setting by income instead of WHO mortality stratum,^[20] and high-income countries were not included in the final analysis. This is supported by O’Ryan et al^[22] estimating that NoV prevalence in Latin America was 15% in the community (95% CI: 11–21%), 14% in outpatient settings (95% CI: 10–19%), and 16% in hospital settings (95% CI: 12–21%).

There are several strengths and potential limitations in the present study. Our systematic review, based on a reasonably large number of studies (178 studies in 46 developing countries worldwide), provided a more probable estimate of NoV prevalence in developing countries by summarizing data with a wide range of estimates and study designs. It also provided the prevalence of NoV GI and GII independently. Weaknesses include the stratification of age into only 2 categories. To determine prevalence in other age groups, such as young adults or the elderly, an additional meta-analysis would need to be performed. In addition, the overall prevalence is potentially overestimated because the data in the pandemic periods 2002 to 2003 and 2006 to 2007, due to the emergence of new GII.4 variants, were included in the analysis, as pointed out by Ahmed et al.^[5] Moreover, as stated above and exemplified in Fig. 1, we could not assess 45 relevant studies, and their exclusion may have biased our results. Finally, since number of cases was not limited in order to collect as many studies as possible in developing countries, some studies reporting a few cases of gastroenteritis may have produced a bias in the estimated prevalence (S2 File. Search strategy, <http://links.lww.com/MD/B884>, S3 File. Data extraction files, <http://links.lww.com/MD/B885>).

In conclusion, the estimated prevalence of NoV in cases of acute gastroenteritis was 17% in developing countries. This review can be used to estimate the burden of NoV-associated

acute gastroenteritis in developing countries, which is currently unclear due to poor diagnosis and surveillance systems, and the estimation may enhance the development of human NoV vaccines.

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