Norovirus and Rotavirus Disease Severity in Children: Systematic Review and Meta-analysis

Margarita Riera-Montes, MD, Miguel O'Ryan, MD,† and Thomas Verstraeten, MD**

Background: Rotaviruses (RVs) and noroviruses (NoVs) are the most common causes of severe acute gastroenteritis in children. It is generally accepted that RVs cause severe acute gastroenteritis in a higher proportion of cases compared with NoVs. To our knowledge, there are no systematic reviews and meta-analyses comparing the severity of NoV and RV disease.

Methods: We searched MEDLINE for studies reporting data for NoV and RV medically attended disease severity in children. We included studies where all children had been tested for both NoV (reverse transcription polymerase chain reaction) and RV (enzyme-linked immunosorbent assay or reverse transcription polymerase chain reaction) and that reported disease severity using the Vesikari or modified Vesikari score, or provided clinical information on severity. We generated pooled estimates of the mean with 95% confidence intervals using random effects meta-analysis.

Results: We identified 266 publications, of which 31 were retained for qualitative analysis and 26 for quantitative analysis. Fourteen studies provided data on severity score for the meta-analysis. The pooled mean severity scores (95% confidence interval) among outpatients were 10 (8–12) and 11 (8–14) for NoV and RV, respectively. Among inpatients, they were 11 (9–13) for NoV and 12 (10–14) for RV. The difference was statistically significant among inpatients, but relatively small (1 point in a 20-point scale). About 20% more children with RV required rehydration when compared with children with NoV.

Conclusions: NoV causes moderate to severe disease similar to RV in young children. This information should be useful for future evaluations of an eventual introduction of NoV vaccines in national immunization programs.

Key Words: norovirus, rotavirus, severity, children

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Globally, rotaviruses (RVs) followed by noroviruses (NoVs) are the most common causes of severe acute gastroenteritis (AGE) in children less than 5 years of age.[1] Both diseases are characterized by vomiting and diarrhea.[2] RV vaccines have been available for several years, with a high impact on the burden of RV disease in those countries where they have been introduced. Studies carried out after the introduction of RV vaccines have shown that NoV has become the major cause of AGE hospitalization in children in countries with widespread use of the RV vaccine.[3–7] Several scales have been developed to assess AGE disease severity, such as the Vesikari score (VS)[8] and its modified versions (modified Vesikari score, MVS)[9,10] and the Clark scale.[11] The Vesikari and the Clark scores were developed to measure AGE disease severity during rotavirus vaccine clinical efficacy trials. Both measure the number and duration of vomiting and diarrhea episodes, and temperature. In addition, the Clark scale measures behavioral symptoms and signs, while the VS measures the presence of dehydration and treatment administered. Studies comparing their use have found them to measure severity very differently, with a majority of cases classified as severe by the VS, being classified as moderate in the Clark score.[12–14] Nakagomi's MVS substitutes the evaluation of treatment by the general level of activity,[10] while Freedman's MVS substitutes the evaluation of dehydration with the level of health care needed.[9] The VS and both MVS have been widely used to estimate severity in AGE in children,[5,9,15–18] while the Clark scale seems to be used rarely. It is generally believed that RV causes severe AGE in a higher proportion of cases compared with NoV.[2] In community-based studies, clinical disease caused by NoV appears to be milder than RV disease; this may be in part because there are proportionally more mild than severe cases of NoV gastroenteritis among prospectively followed children.[19,20]

NoV vaccines are currently under development, and disease severity will be an important aspect to be considered by decision-makers when assessing the need for introduction of any eventual NoV vaccine in the national immunization programs. To our knowledge, there are no systematic reviews published in the literature comparing the severity of NoV and RV disease. Therefore, we performed a systematic literature review and meta-analysis of the existing literature to compare the severity of NoV and RV disease in children to provide useful information for future evaluations of eventual introduction of NoV vaccines into national immunization programs.

METHODS

Search Strategy and Selection Criteria

We carried out a literature search of MEDLINE (via PubMed) using the following search terms (norovirus* OR Norwalk OR calicivirus* OR "small round virus" OR "small round viruses") AND (rotavirus*) AND (severity OR score OR symptom* OR clinical) AND (child* OR infant* OR pediatric* OR pediatrics [MesH]). No filters, language or date restrictions were applied. Two reviewers (M.R.M., M.B.) screened titles and abstracts for relevance. Original articles were obtained and assessed for eligibility. Bibliographies of articles identified in the search were scanned for additional references. We applied the following eligibility criteria: (1) all children must have been tested for NoV and RV; (2) the NoV diagnosis must have been established by reverse transcription polymerase chain reaction; and (3) disease severity must have been calculated by VS or MVS for both NoV and RV infection OR the study must provide information about at least one of the following severity parameters: mean number of stools per day, mean duration of diarrhea, mean number of vomiting episodes per day, mean duration of vomiting, mean maximum temperature and proportion of subjects requiring

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From the *P95 Epidemiology and Pharmacovigilance, Leuven, Belgium; and †Programa de Microbiología e inmunología, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile.

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Address for correspondence: Miguel O'Ryan, MD, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Avda Independencia 1027, Santiago de Chile, Chile. E-mail: moryan@med.uchile.cl.

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intravenous rehydration. We excluded studies that did not provide the total number of NoV-positive and RV-positive subjects for which information on the severity parameters was available.

Data Extraction and Bias Assessment

Relevant data were extracted by one reviewer (M.R.M.) from the selected studies and tabulated in a spreadsheet (MS Excel) specifically developed for this review. The following information was extracted for each study: first author, title, journal, year of publication, country, year(s) of data collection, study description, setting (outpatient, inpatient), age group, case definition of AGE, diagnostic method used, number of cases tested, number of cases positive for NoV or RV, number of NoV-positive and RV-positive cases for which information on severity parameters was available, mean or median estimate with standard deviation (SD) or range for all the severity parameters of interest. Data were stratified by medical setting and age group. If the study provided data for more than one setting or more than one age group, data were extracted separately for each stratum. For the medical setting, we stratified data into 4 categories: inpatient; outpatient, including outpatients and emergency department at hospitals and primary care clinics; community, including community cohort studies; and other settings, including studies in which the setting was not described or in which a mixture of settings was included but stratified data were not reported. For age, we grouped studies into 2 categories: younger than 6 years and mixed (studies that included children 6 years of age and older and provided no further age stratification).

Meta-analysis

The data were pooled for analysis by severity parameter, virus, age group and setting. VS and MVS were reported as mean or median. For those studies where the median and range were reported, we used these to estimate the mean and SD following the method described by Hozo et al.[21] For those estimates where only the interquartile range was provided, we divided the interquartile range by 1.35 to estimate the SD.

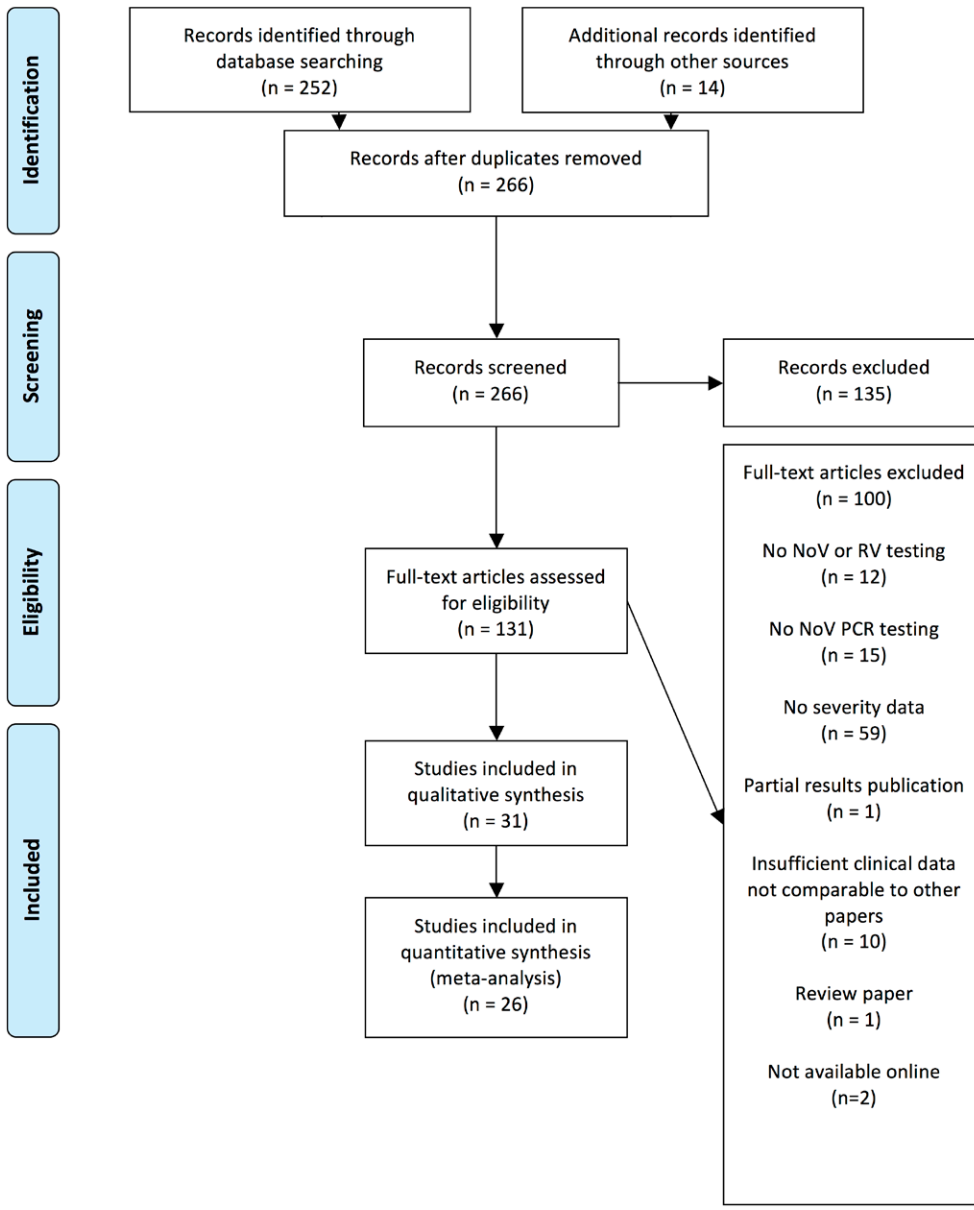

FIGURE 1. Flow diagram of the literature review selection process. full color online

Studies that did not provide the SD, range or interquartile range were included in the narrative review but excluded from the meta-analysis. We generated pooled estimates of the mean with 95% confidence intervals (95% CI) by fitting random effects meta-analysis models using the restricted maximum likelihood method. We calculated the I^2 statistic as a measure of the proportion of the overall variation that was attributable to interstudy heterogeneity. We then compared the severity parameters between RV and NoV using the χ^2 test with a 0.05 significance level. All analyses were conducted with the statistical software R.

RESULTS

We carried out the database search on May 7, 2016, retrieving 252 records. A further 14 records were identified from screening the reference list of selected publications. We discarded 135 records as not relevant after title and abstract screening, leaving 131 full-text records to be assessed for eligibility. Of these records 100 were excluded, leaving 31 records to be included in the systematic review and 26 to be included in the meta-analysis of at least one severity parameter (Fig. 1). The selected records comprised studies from 17 different countries from Europe, the Americas, Asia, North Africa and the Middle East[15–18,20,22–47] providing severity information on 2076 subjects with NoV disease and 4000 subjects with rotavirus disease recruited between 1993 and 2012 (Table, Supplemental Digital Content 1, http://links.lww.com/INF/C867). The proportion of subjects positive for NoV ranged from 6% to 34%, and for RV from 15% to 66%. All but 4 studies were carried out before RV vaccine introduction in the respective countries. No data sources were identified for the community setting, so results are presented only for outpatient, inpatient and mixed settings.

Vesikari and Modified Vesikari Severity Score

The mean NoV scores ranged from 7 to 16, and the mean RV scores from 8 to 18 for all settings and age groups. The scores were higher among inpatients compared with outpatients.

The overall mean severity scores were 11 for NoV (95% CI: 9–12) and 12 for RV (95% CI: 11–13) (Table 1, Fig. 2A and B). These overall values were statistically significantly different, as were the scores for inpatients: 11 for NoV (95% CI: 9–13) and 12 for RV (95% CI: 10–14). Values for outpatients were not statistically significantly different: 10 for NoV (95% CI: 8–12) and 11 for RV (95% CI: 8–14). Results stratified per age group were similar, with slightly higher scores for both pathogens in studies that focused on children under 6 years of age (11 [95% CI: 9–13] for NoV and 13 [95% CI: 10–15] for RV (Fig. 2C and D).

We carried out a sensitivity analysis including only the 12 studies that used the original VS. In this case, the scores were slightly lower for both NoV and RV.

The overall mean VS was 10 (95% CI: 9–11) for NoV and 12 (95% CI: 10–13) for RV. The mean scores for inpatients were 10 (95% CI: 9–12) and 12 (95% CI: 10–14) for NoV and RV, respectively, while for inpatients, the mean scores were 9 (95% CI: 7–11) for NoV and 10 (95% CI: 9–11) for RV. The differences observed overall and in inpatients were statistically significant while the difference in outpatients was not.

Severity Parameters

The results are summarized in Table 1. Most severity parameters showed small or no differences between the NoV and RV groups, with the exception of the need for intravenous rehydration. Approximately 18%–19% more RV patients required intravenous rehydration, compared with NoV patients. This difference was seen for both outpatients and inpatients. Some significant differences were seen for a few other parameters, with the severity always being higher in the RV patients, but the differences were generally small on an absolute scale.

DISCUSSION

We report the first systematic literature review comparing the severity of NoV and RV disease among children. There was no significant difference in the severity score of RV and NoV AGE cases presenting as outpatients. Among inpatients, the difference in severity between RV and NoV AGE cases, while statistically significant, was relatively small (1 point on a 20-point scale) and of unclear clinical significance. When looking at differences in the individual elements that make up the VS and MVS, there were limited differences between the 2 diseases in all severity parameters except for the proportion of subjects requiring rehydration. We found 18%–19% more children with RV required rehydration compared with NoV. The severity scores were higher for both NoV and RV when only studies including children under the age of 6 were analyzed.

Our study had several limitations. There was a high heterogeneity between studies ($I^2 > 95\%$), which may reflect real differences in severity between countries, different standards in the application of the score definitions, differences in disease management, socioeconomic differences and access to health care. This may have also been affected by the use of the original VS or its modified versions. When limiting the analysis to studies that used the original VS only, the estimated scores were slightly lower for both NoV and RV without affecting the statistical significance. Some NoV genotypes are expected to result in more severe

TABLE 1. Results of the meta-analysis per severity criteria for NoV and RV, overall and per setting

				Setting					
				Outpatient		Inpatient		Overall	
Severity Parameter	N Studies (N=26)	Sample Size, NoV (N=2076)	Sample Size, RV (N=4000)	NoV Mean (95% CI)	RV Mean (95% CI)	NoV Mean (95% CI)	RV Mean (95% CI)	NoV Mean (95% CI)	RV Mean (95% CI)
VS	14	977	2127	10 (8–12)	11 (8–14)	11* (9–13)	12* (10–14)	11* (9–12)	12* (11–13)
Number of daily stools	17	1583	2844	5* (5–6)	6* (5–7)	6* (5–7)	6* (5–7)	6* (5–6)	6* (6–7)
Duration of diarrhea (d)	15	1559	2464	3 (2–4)	3 (2–5)	4 (3–6)	4 (4–5)	4 (3–5)	4 (4–5)
Number of daily episodes of vomiting	17	1583	2844	3 (2–4)	3 (3–4)	4 (2–5)	4 (2–5)	3 (3–4)	4 (3–4)
Duration of vomiting (d)	15	1559	2464	2* (1–2)	2* (1–3)	2 (2–3)	2 (2–3)	2 (2–2)	2 (2–3)
Max temp (°C)	11	1142	1997	37.6* (37.0–38.3)	37.8* (37.0–38.6)	38.5* (37.8–39.2)	38.8* (38.2–39.3)	38.3 (37.8–38.8)	38.4 (38.0–38.9)
Proportion requiring intravenous rehydration (%)	6	331	728	33 (14–56)	49 (11–87)	54* (1–95)	75* (4–97)	42* (18–68)	60* (36–83)

*Mean difference between NoV and RV statistically significant, $P < 0.05$.

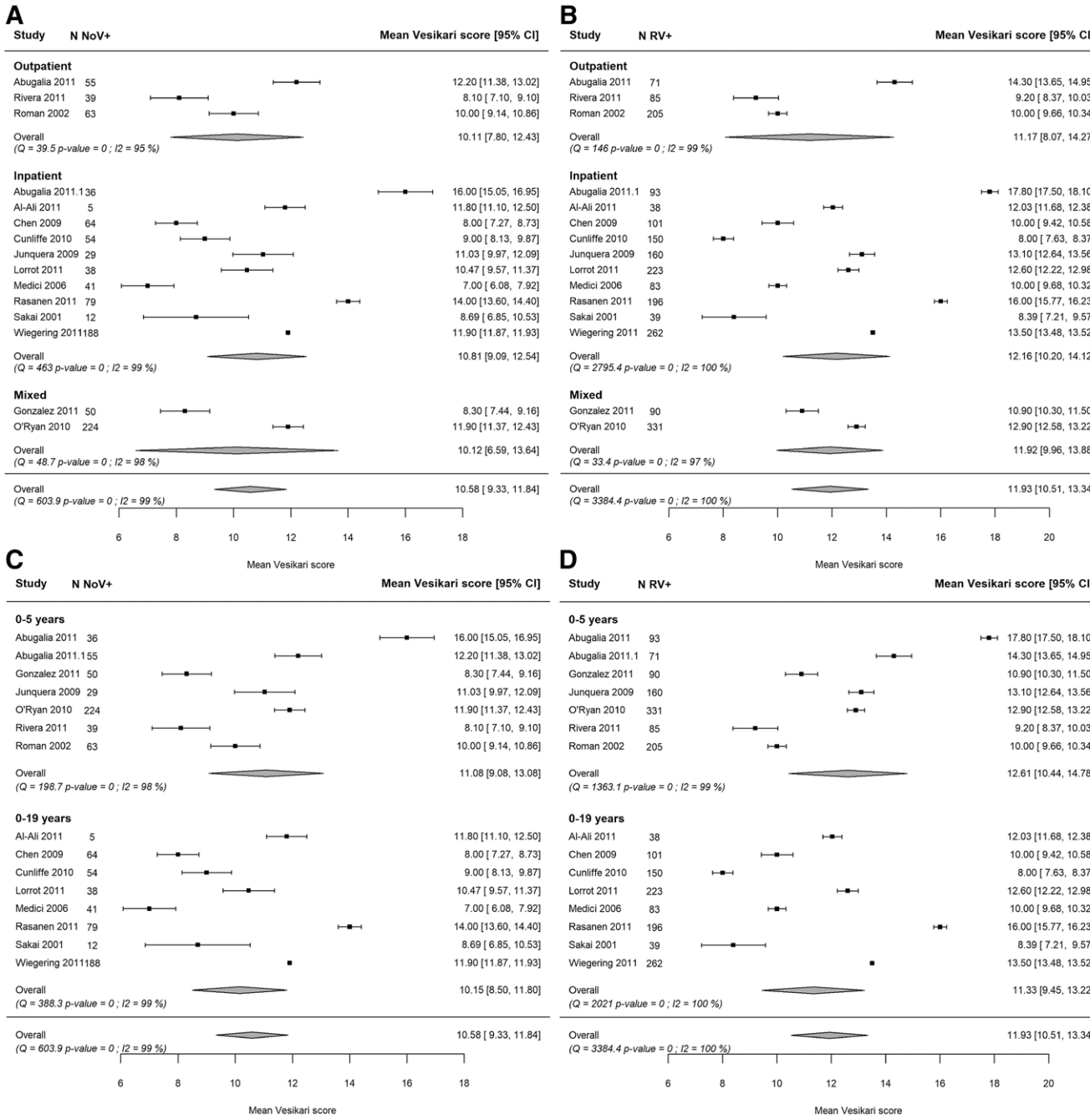

FIGURE 2. Forest plot of the mean VS for (A) NoV, overall and stratified per setting; (B) RV, overall and stratified by setting; (C) NoV, overall and per age group; and (D) RV, overall and per age group.

disease compared with other types.[48] We did not find sufficient type-specific information to compare RV severity with different NoV genotypes.

CONCLUSIONS

In conclusion, in an increasing number of countries, NoV is now the most common cause of pediatric gastroenteritis requiring medical attention and causes moderate to severe AGE similar to RV with somewhat lower fever and around 20% less need for rehydration. Once a safe and effective NoV vaccine is available for pediatric use, this information should be a useful addition to the burden of disease data when evaluating the utility of vaccine introduction in national immunization programs.

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