Vaccine 33 (2015) 4065–4068

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Brief report

Global age distribution of pediatric norovirus cases

Kayoko Shioda[a,b,*], Anita Kambhampati[a,b], Aron J. Hall[a], Ben A. Lopman[a]

[a] National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30329, USA
[b] Oak Ridge Institute for Science and Technology, Oak Ridge, TN 37831, USA

ARTICLE INFO

Article history:
Received 21 April 2015
Received in revised form 19 May 2015
Accepted 21 May 2015
Available online 4 June 2015

Keywords:
Norovirus
Gastroenteritis
Age distribution
Vaccines
Vaccine
Socioeconomic factors

ABSTRACT

Norovirus is increasingly recognized as a major cause of acute gastroenteritis among children <5 years of age. We searched for publications that reported detailed age distributions of pediatric norovirus cases, and assessed associations between age distribution and socio-demographic factors to identify the most critical age periods to prevent norovirus cases among young children. Approximately 70% of pediatric norovirus cases occurred between 6 and 23 months of age. A younger age distribution was found in lower income countries and inpatient settings. These findings suggest that a norovirus immunization schedule completed by 6 months could have the potential to prevent about 85% of pediatric cases, while a vaccine delivered at 12 months of age would only have the potential to prevent about 50% of pediatric cases. With a younger age distribution in lower income settings, early prevention would be even more critical.

1. Introduction

With the substantial decline of rotavirus-associated diarrhea in countries that have introduced rotavirus vaccines, norovirus is increasingly recognized as a main cause of acute gastroenteritis (AGE) [1,2]. Norovirus vaccines are under development and have shown promise in safety and immunogenicity studies, as well as protection against infection and disease in experimental challenge studies [3,4]. Young children have the highest incidence of norovirus gastroenteritis [5,6], so stand to benefit from a vaccine. However all vaccine studies have been performed among adults. For development of a pediatric vaccine, a number of specific questions will arise, including the number of doses required, the acceptability of an adjuvant, and the appropriate age to vaccinate. To identify the most critical age periods to prevent norovirus among young children, we conducted meta-analysis to understand the detailed age distribution of pediatric norovirus AGE cases (defined as children aged <5 years).

2. Methods

We used the database described in a previous systematic review [7] that included studies published between January 1997 and March 2014; we updated the literature search to include studies published between March 1, 2014, and August 31, 2014 in the Medline database. We searched for studies using the search term "norovirus." Two individuals reviewed titles and abstracts and obtained full articles if studies were deemed relevant to our research. Studies that met all four of the following criteria were included: (1) recruited patients with AGE symptoms from a specific geographic area or group of people; (2) used PCR to detect norovirus in stool; (3) done continuously for ≥1 year; and (4) reported the age distribution among laboratory-confirmed pediatric norovirus cases.

2.1. Summary of age distributions

Data on the total number of cases and the number of cases in each age group were extracted from each study. After trying various categorizations (Supplementary Table/Figs. 1 and 2), the following four age groups were used for analyses: <6, 6–11, 12–23, and 24–59 months.

The cumulative proportion of pediatric norovirus cases by age was calculated for each study. We pooled this cumulative proportion of cases and calculated a weighted average. The following

* Corresponding author at: National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA 30333, USA. Tel.: +1 404 639 0002.
E-mail addresses: yji4@cdc.gov (K. Shioda), wyc4@cdc.gov (A. Kambhampati), esg3@cdc.gov (A.J. Hall), iow4@cdc.gov (B.A. Lopman).

http://dx.doi.org/10.1016/j.vaccine.2015.05.051
0264-410X/

formula shows the weighted average of the cumulative proportion of pediatric norovirus cases by the age of 6 months:

$$= \frac{\sum_i (Cases_i * P(Cases\,0-5m)_i)}{\sum_i Cases_i}$$

where $P(Cases\ 0-5m)_i$ is the proportion of pediatric norovirus cases that were among the <6 month age group and $Cases_i$ is the total number of norovirus cases aged 0–59 months in study *i*. $\sum_i Cases_i$ is the sum of all norovirus cases 0–59 months of age for all included studies. Similar formulae were used to calculate weighted average for <12 and <24 month age groups.

2.2. Association of age distribution with socio-demographic factors

Per capita gross domestic product (GDP) of each country from the year of publication was used as an indicator of income level [8]. Countries were additionally categorized into three levels of development according to World Health Organization (WHO) mortality strata [9]: high-mortality developing (HMD), low-mortality developing (LMD), and developed. The study settings were grouped into inpatient (including emergency departments), outpatient, community, and other. The "other" category included studies in which setting was not described or a mixture of settings was included but stratified data were not reported.

We used meta-regression analyses to evaluate associations between potential predictors (i.e., income level and development index of each country and study setting) with the proportion of pediatric cases that occurred in the <12 month age group. We selected this age limit as the outcome because the largest variation in cumulative proportion of cases across socio-demographic factors was observed at 12 months. Mixed-effects models were fitted using restricted maximum-likelihood estimation, with the number of pediatric norovirus AGE cases in each study as weights and "study" as a random effect. We assumed that per capita GDP and WHO mortality strata would indicate similar levels of development; thus we fit a multivariate mixed-effects model with per capita GDP and study setting. All analyses were performed using the package "metafor" in R [10,11].

3. Results

We identified 78 studies about pediatric norovirus from the previously developed database [7]. We also identified 261 publications

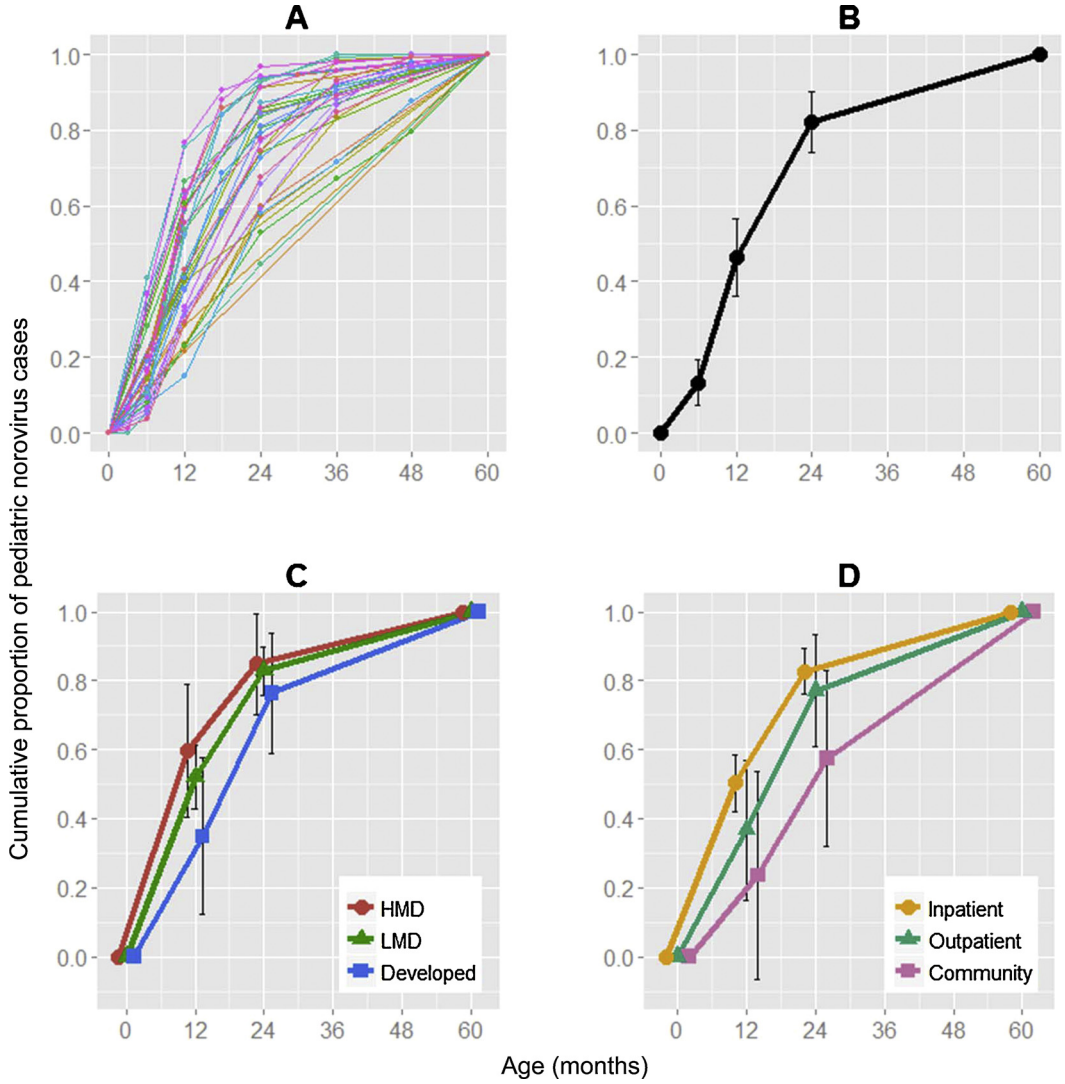

Fig. 1. Cumulative proportion of pediatric norovirus cases (A: 35 individual studies, B: weighted average of cumulative proportion, C: weighted average of cumulative proportion stratified by country development level, D: weighted average of cumulative proportion stratified by study settings). *Abbreviations*: HMD high mortality developing countries; LMD low mortality developing countries.