Epidemiology of Rotavirus in the Iranian Children: A Systematic Review and Meta-analysis

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Abstract

Rotavirus is associated with increased risk for severe diarrhea in infants and young children worldwide. This systematic review and meta-analysis was performed to determine the prevalence rate of rotavirus from different parts of Iran and provide an overall relative frequency (RF) for Iran. We performed a systematic literature review from several databases including PubMed, ISI Web of Science, Scopus, OVID, MAG IRAN, IranMedex, and Iranian Scientific Information Database. We searched the following keywords: “rotavirus,” “rotavirus infection,” “acute gastroenteritis,” “diarrhea,” “children,” “infant,” and “Iran.” The purpose of this study was to report the prevalence of rotavirus with the application of meta-analysis. We selected 43 researches out of 1147 for our study. From all the samples, the pooled estimate of prevalence (95% confidence interval) =39.9% (0.396%–0.409%) were rotavirus positive. It should be noted that rotavirus infection’s RF varied from 6.4% to 79.3% in Birjand and Tehran Provinces, respectively. Thereupon, it is divergent in different studies. According to our study result, rotavirus RF has a wide range in Iran and is associated with diarrhea in children. Thus, further researches should be taken to minimize the emergence and transmission of rotavirus.

Keywords: Children, diarrhea, infant, Iran, rotavirus, rotavirus infection

Introduction

Rotavirus is a member of the Reoviridae family. Its genome is a segmented double-stranded RNA (composed of 11 pieces) and this virus has an icosahedral double-layer capsid.[1,2] The virus is classified into G and P serotype based on VP7 and VP4 proteins, respectively.[3,4] Rotavirus infects villus epithelial cells of the small intestine without any effect on gastric mucosa and colon. The virus replicates in the cytoplasm of these cells and thus impairs transport of nutrients.[5] Rotavirus can be spread easily from person to person through contaminated hands and fomites. Among infectious diseases worldwide, gastroenteritis is the third leading cause of death which brings (about 527,000 losses of life) among children annually.[6] It is estimated that only 20% of gastroenteritis is caused by bacterial agents and the rest caused by viruses. The most important viral agents that lead to acute gastroenteritis include rotavirus, astrovirus, adenovirus, and Norwalk virus, in which rotavirus is more common than the others, especially in Asia [Figure 1a and b].[2,7,4] Rotavirus is a major cause of severe childhood diarrhea and is associated with morbidity and mortality in infants and young children worldwide.[9] In developing countries, rotavirus infection gives rise to 82% of deaths that is because of malnutrition or lack of access to rehydration therapy.[10] Recent studies have estimated that gastroenteritis is responsible for 17% of mortality among children under 5 years old worldwide.[11] Primary symptoms of rotavirus infection include vomiting, fever, watery diarrhea, and abdominal pain; sometimes, exacerbation leads to severe dehydration which requires hospitalization.[12] Rotavirus detection in stool samples of children suffering from gastroenteritis can be assessed by different laboratory methods such as enzyme-linked immunosorbent assay (ELISA), latex

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Vaccines are the most effective tool that can prevent infection, especially in developing countries; therefore, an increased understanding of the epidemiology and seasonal patterns is needed to ensure vaccine efficacy and effectiveness for intervention programs. Determination of annual epidemics in children can be a good way to treat and prevent unnecessary actions, such as prescribing antibiotics in cases of viral acute gastroenteritis. In this study, we systematically reviewed published data on the prevalence rate of rotavirus in different parts of Iran, and using meta-analysis, we provide an overall relative frequency (RF) for our country.

**Methods**

**Search strategy**

We searched PubMed, ISI Web of Science, and Scopus (up to January 2015) databases using the following keywords: “rotavirus,” “rotavirus infection,” “acute gastroenteritis,” “diarrhea,” “children,” “infant,” and “Iran” [Table 1]. In addition to English articles, two Persian scientific search engines including “The Iranian Scientific Information Database” (www.sid.ir) and “IranMedex” (www.Iranmedex.ir) were searched as well for relevant articles. Furthermore, reference lists of all related studies were reviewed for any other related publication. Our search was restricted to the original articles/abstracts published in English and Persian which reported the prevalence of rotavirus by enzyme immunoassay (EIA), LA, EM, polyacrylamide gel electrophoresis (PAGE), and molecular methods such as reverse transcription polymerase chain reaction (RT-PCR) in Iran.

**Inclusion criteria**

Included studies (in English and Persian) used in this meta-analysis and systematic review must meet the following criteria: (A) rotavirus samples (stool) were collected from the Iranian children because this review study is limited to the Iran’s population and measured the rotavirus prevalence in children only, (B) studies which involved children up to 6 years of age, (C) assays such as EIA, LA, EM, or PAGE and molecular methods such as RT-PCR were incorporated to detect rotavirus because these are approved and acceptable laboratory methods for rotavirus.

**Exclusion criteria**

Articles were excluded from this review if (A) samples were partially/totally selected from rotavirus and were archived before, (B) studies which used other methods instead of standard tests to identify rotavirus, (C) laboratory studies that had been done on animals, (D) congress abstracts, review articles, studies reported in languages other than English or Persian, meta-analysis, or systematic reviews and duplicate publication of the same study (or published both in English and Persian), except duplicate studies in which more sample size and more detailed results were provided.

**Data collection**

Data were extracted from studies based on title, abstract, and keywords by two researchers, independently. Disagreements were resolved by consensus of the whole team in both phases.

**Assessment of quality studies**

We used checklist and diagram of the PRISMA, and then critical appraisal has been done by STROBE form. PRISMA and STROBE can also be used as a basis for reporting systematic reviews of other types of research; STROBE particularly evaluated the prevalence for any outcome.

**Statistical analysis**

The numbers of total participants and participants with rotavirus were used to estimate the RF which was then converted to log RF and its standard error for the meta-analysis. The pooled prevalence was derived by random-effect model that takes between-study variation into account. The heterogeneity and the variation in pooled estimation were assessed by using Cochrane’s $Q$-test and $I^2$, respectively. To examine the value which the pooled prevalence might depend on, sensitivity analysis was used for a particular study or a group of publications. Publication bias was checked by Begg’s funnel plots and asymmetry tests including Egger’s regression asymmetry test and Begg’s adjusted rank correlation test. All statistical analyses were performed using STAT 11.0 (STATA Corp, College Station, TX, USA), and $P < 0.05$ was considered statistically significant.

**Results**

A total of 1147 articles were retrieved by database search. A summary of the literature search and study selection is showed in Figure 2. In a secondary screening process, 1020 publications were excluded based on title and abstract evaluations, and 127 articles were retained for detailed full-text
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The prevalence of rotavirus in Iran was estimated at 39.9% (95% confidence interval) = (0.396%–0.409%) [Figure 3]. However, evident heterogeneity of rotavirus was observed among several studies (Cochran’s Q-test, P < 0.001 and I² = 98.7%). Figure 3 shows the forest plot of rotavirus meta-analysis. Sensitivity analysis was performed by sequential omission of individual studies. The combined RFs of the prevalence rate of rotavirus from sequential omission were not altered after omission (with the average 35.3%), indicating that our results were statistically robust.

**Discussion**

In this study, the published and unpublished information for the last 30 years about the rotavirus in the Iranian children (especially in children <5 years of age) were collected. The majority of these studies were published after 2000. The high prevalence of rotavirus infections in different parts of Iran, importance of rotavirus in children and association with gastroenteritis, morbidity, and mortality has led us to do this meta-analysis and systematic review. The present study designed to estimate the prevalence and distribution of rotavirus infection in Iranian children according to available data from articles collected from different parts of our country. Recently, Iranian researchers have done different studies to detect rotavirus and to report epidemiology and importance of this virus in children’s health. According to our study, the mean prevalence of rotavirus in Iran was 39.9%, which showed that 50% of Iranian cities were afflicted. We tried to compare our study with several other studies, carried out in different parts of the world. According to the recent studies, increased worldwide detection rate in rotavirus among children aged <5 years in 1986–1999 was 20%, 1990–2004 was 29%, and in 2001–2008 was 40%. Different studies have been performed for investigation of rotavirus in the world. WHO reported that gastroenteritis caused by rotavirus which occurred in Iran, Iraq, Syria, Egypt, Oman, Jordan, Yemen, Libya, Morocco, and Tunisia was 42%. Malek et al. indicated that the rate of rotavirus diarrhea (in children) in Eastern Mediterranean Region was 40%. In addition, results of this study revealed high percentage of rotavirus gastroenteritis in Syria (61%) and Oman (51%) and lowest percentage in Saudi Arabia, Tunisia, and Egypt (16%–23%). Rotavirus infection rate was 20%–30% in some Asian countries including Hong Kong, India, Bangladesh, and South Korea, but it was

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Figure 2: Flow diagram for study selection progress
Table 2: Characteristics of Studies Included in the Systematic Review and Meta-analysis after Full Evaluation

| First author | Year | Study location          | Total number of samples | Rotavirus proportion (%) | Type of sample | Laboratory method                      | Genotyping | Reference |
|--------------|------|-------------------------|-------------------------|--------------------------|----------------|----------------------------------------|------------|-----------|
| Amini        | 1990 | Tehran                  | 915                     | 25                       | Stool          | Hemagglutination, latex agglutination  | NR         | [16]      |
| Saeb         | 1997 | Tehran, Zahedan         | 450                     | 16.2                     | Stool          | ELISA                                  | NR         | [17]      |
| Habibi       | 2004 | Tehran                  | 180                     | 36.6                     | Stool          | ELISA                                  | G1, G4     | [18]      |
| Moradi       | 2001 | Zahedan                 | 171                     | 29.2                     | Stool          | ELISA                                  | NR         | [19]      |
| Khalili      | 2004 | Shahrekord              | 245                     | 78                       | Stool          | ELISA, RT-PCR, EM                      | G1         | [7]       |
| Modares      | 2005 | Tehran                  | 1250                    | 32.3                     | Stool          | RNA PAGE, latex agglutination           | NR         | [20]      |
| Kordidarian  | 2007 | Isfahan                 | 80                      | 26.2                     | Stool          | Latex agglutulation                     | NR         | [21]      |
| Kazemi       | 2006 | Isfahan                 | 185                     | 30.8                     | Stool          | ELISA                                  | NR         | [22]      |
| Zarnani      | 2004 | Tehran                  | 704                     | 15.3                     | Stool          | ELISA                                  | NR         | [23]      |
| Samarbazadeh | 2005 | Ahwaz                   | 137                     | 26.2                     | Stool          | dsRNA-PAGE                             | NR         | [24]      |
| Samarbazadeh | 2005 | Ahwaz                   | 63                      | 36.5                     | Stool          | dsRNA-PAGE                             | NR         | [24]      |
| Kazemi       | 2007 | Zanjan                  | 400                     | 31.5                     | Stool          | ELISA                                  | NR         | [25]      |
| Taremi       | 2005 | Tehran                  | 372                     | 25.2                     | Stool          | ELISA                                  | G1         | [26]      |
| Hamkar       | 2008 | Mazandaran              | 400                     | 62                       | Stool          | ELISA                                  | NR         | [27]      |
| Eesteghamati | 2009 | Tabriz, Mashhad, Tehran, Shiraz, Bandar Abbas | 2198 | 59.1 | Stool | ELISA, G4, G1, G2                      | NR         | [28]      |
| Savadkoohi   | 2007 | Babol                   | 208                     | 60.5                     | Stool          | ELISA                                  | NR         | [29]      |
| Kargar       | 2012 | Shiraz                  | 138                     | 34.7                     | Stool          | ELISA                                  | NR         | [30]      |
| Emanghorashi | 2015 | Jahrom                  | 102                     | 67.6                     | Stool          | ELISA, latex agglutination             | NR         | [31]      |
| Farahraj     | 2007 | Tehran                  | 374                     | 24.5                     | Stool          | ELISA                                  | G1         | [32]      |
| Najafi       | 2012 | Shiraz                  | 138                     | 34.7                     | Stool          | ELISA, RT-PCR                          | NR         | [33]      |
| Zaraei-Mahmoodabadi | 2009 | Tehran | 193 | 79.2 | Stool | ELISA                                  | NR         | [34]      |
| Zaraei-Mahmoodabadi | 2009 | Tehran | 67 | 20.8 | Stool | ELISA                                  | NR         | [34]      |
| Yahyapour    | 2008 | Babol                   | 200                     | 50                       | Stool          | ELISA                                  | NR         | [35]      |
| Sadeghian    | 2010 | Mashhad                 | 156                     | 28.8                     | Stool          | ELISA, latex agglutination             | NR         | [36]      |
| Kargar       | 2008 | Tehran                  | 260                     | 34.6                     | Stool          | ELISA                                  | NR         | [37]      |
| Sanaee       | 2009 | Tabriz                  | 213                     | 53                       | Stool          | ELISA                                  | G4, G1     | [12]      |
| Taheri       | 2010 | Birjand                 | 311                     | 61.4                     | Stool          | ELISA                                  | NR         | [38]      |
| Manesh       | 2011 | Tehran                  | 150                     | 19.3                     | Stool          | dsRNA-PAGE                             | G1, G4     | [39]      |
| Maleki       | 2010 | Kerman                  | 118                     | 24.6                     | Stool          | Gel electrophoresis                    | NR         | [40]      |
| Kargar       | 2011 | Borazjan                | 375                     | 24.2                     | Stool          | ELISA                                  | G1, G4, G9 | [41]      |
| Hamkar       | 2008 | Mazandaran              | 353                     | 63.7                     | Stool          | ELISA                                  | NR         | [27]      |
| Moradi       | 2010 | Gorgan                  | 411                     | 53                       | Stool          | SDS-PAGE                               | NR         | [42]      |
| Kargar       | 2013 | Marvdasht               | 141                     | 28.3                     | Stool          | ELISA                                  | G1, G2, G4 | [43]      |
| Khoshdel     | 2014 | Shahrekord              | 100                     | 30                       | Stool          | RT-PCR                                 | G1, G9     | [44]      |
| Rahbarimanesh AA | 2011 | Tehran | 700 | 19 | Stool | dsRNA-PAGE                             | G1, G4, G8 | [45]      |
| Ghorashi     | 2011 | Tabriz                  | 511                     | 55.6                     | Stool          | ELISA                                  | NR         | [46]      |
| Kargar       | 2010 | Jahrom                  | 163                     | 46                       | Stool          | ELISA                                  | G1, G4     | [47]      |
| Hassanzadeh  | 2001 | Shiraz                  | 220                     | 11.3                     | Stool          | EM                                     | NR         | [48]      |
| Moghim       | 2012 | Isfahan                 | 150                     | 12.6                     | Stool          | dsRNA electrophoretypes                | NR         | [49]      |
| Jadali       | 2013 | Tehran, Shiraz, Tabriz, Bandar Abbas, Mashhad | 2988 | 55.4 | Stool | ELISA                                  | NR         | [50]      |
| Kajbaf       | 2012 | Ahwaz                   | 180                     | 35                       | Stool          | ELISA                                  | NR         | [51]      |
| Motamedifar  | 2013 | Shiraz                  | 827                     | 42                       | Stool          | ELISA                                  | NR         | [52]      |
| Kargar       | 2014 | Yasuj                   | 184                     | 28.2                     | Stool          | ELISA, RT-PCR                          | G1, G2, G4, G8 | [53] |

NR: Not reported, ELISA: Enzyme-linked immunosorbent assay, RT-PCR: Reverse transcription polymerase chain reaction, EM: Electron microscopy, PAGE: Polyacrylamide gel electrophoresis, SDS: Sodium dodecyl sulfate
43%–58% in China, Vietnam, Japan, Taiwan, Myanmar, and Thailand. Latipov et al. showed rotavirus positivity in Central Asia region (2011) including Kazakhstan (15%), Uzbekistan (49%), and Kyrgyzstan (36%). In the study carried out by Akan et al. (2009) in Turkey, the prevalence of rotavirus was 18.7%. In another study by Podkolzin et al. carried out in Russia, the rotavirus proportion was 44%. Various recent studies showed the proportion of rotavirus infection in Latin America (30%), Europe (40%), and Africa and Middle East (34%–40%). Bwogi et al. detected rotavirus in 37% (263/712) of the children in Uganda (2012–2013). Khoury et al. showed that the proportion of rotavirus gastroenteritis in Iran and Egypt has increased over time (15% in 2003–2004 vs. 59% in 2005–2006). Some locations of Iran have higher proportions of rotavirus infection such as Tehran, Shahr-e Kord, Mazandaran, Jahrom, and Babol Provinces. Proportion of rotavirus infection varied from 6.3% in Birjand to 78% in Shahr-e Kord and 79.2% in Tehran. These diversities might be due to the time and seasonal differences, geographical locations, age and gender of patients, and various laboratory methods to detect the virus. Among 43 studies that reported seasonal outbreak, 29 of them (~67.4%) have shown increased disease prevalence in cold seasons and also in some countries including Pakistan, Saudi Arabia, and Tunisia; this prevalence is high in cold seasons. Malek et al. demonstrated Egypt and Iran rotavirus infection had not followed any seasonal trend, while we showed that this infection is seasonally distributed (cold season) in Iran. The results of this meta-analysis show that the most common types of Iran are G1 and G4. These types are more similar to the identified types of Europe. In Turkey, G1 has increased in the same as Iran while G4 type has decreased; however, in Saudi Arabia, G2 has increased. In a 10-year period (2000–2009), types that have circulated in Asia were G1 (23.6%), G2 (11.8%), G3 (18.9%), and G9 (7.4%); in addition, mixed rotavirus strains (7.5%), less common strains (16.8%), and nontypeable strains (14.0%) have been seen. G1, G2, G3, and G9 are common strains (about 80% of circulating types) in Taiwan, Japan, and Mongolia. Furthermore, G1, G2, and G9 are circulating types in India, China, Bangladesh, South Korea, Vietnam, and Indonesia. It is noteworthy that some uncommon types such as G12 were detected in certain countries such as India. It is very important to determine circulating rotavirus strains in order assess the impact of Rotavirus vaccines. Therefore, it is necessary to perform analytical epidemiologic studies to determine complement routine strain surveillance for vaccination programs. In most of the studies (that have used in our review), ELISA was used for rotavirus detection. This method has high sensitivity and specificity. Therefore, using ELISA assay can reduce the bias in virus detection. The findings showed that the prevalence and distribution of rotavirus infection in developed countries was lower than developing countries; thus, health-care systems and physicians may face difficulties to treat and control the infection in developing countries. There were several limitations that should be considered in our meta-analysis including (1) non-English literature reviews that had language obstacle, (2) missed studies, due to limited access to the in press articles; however, the funnel plot suggests that publication bias was not obvious, (3) no data on rotavirus infections in some
parts of Iran such as west part, (4) heterogeneity among the included studies. In conclusion, this meta-analysis revealed that rotavirus was associated with gastroenteritis in Iranian children, and also, we demonstrated an epidemiologic picture of rotavirus infection in our country. This study provides information about circulating types in different geographical areas of Iran. Careful monitoring of rotavirus infection and early detection using sensitive and specific laboratory methods are recommended for prevention and control of rotavirus infection in the Iranian children.

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**Conflicts of interest**

There are no conflicts of interest.

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