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 vir*us*, in which rotavirus is more common than the others, especially in Asia [Figure 1a and b].[2,7,8] 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

Access this article online	
Quick Response Code:	**Website:** www.jgid.org
	DOI: 10.4103/0974-777X.205173

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How to cite this article: Monavari SH, Hadifar S, Mostafaei S, Miri A, Keshavarz M, Babaei F, *et al*. Epidemiology of rotavirus in the Iranian children: A systematic review and meta-analysis. J Global Infect Dis 2017;9:66-72.

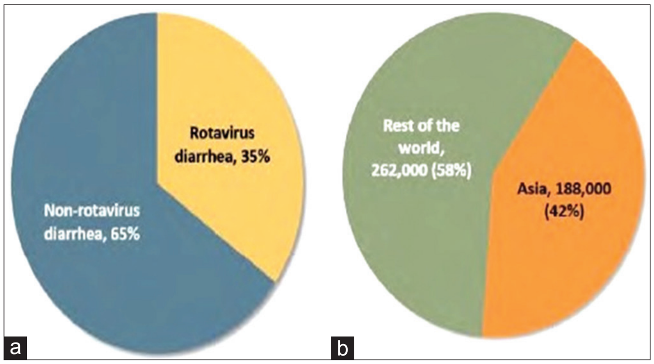

Figure 1: (a) Hospitalizations due to diarrhea in Asian children under 5 years old. (b) Global deaths of rotavirus in children under 5 years of age

agglutination (LA), electron microscopy (EM), and molecular methods.[13,14] 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.[15] 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.

Table 1: Search Strategy

("Rotavirus" [MeSH Terms]) AND ("Rotavirus infection" [MeSH Terms]) AND ("Children" [MeSH Terms]) AND ("Infant" [MeSH Terms]) AND ("Acute gastroenteritis" [Text Word]) AND ("Diarrhea" [MeSH Terms]) AND ("Iran" [MeSH Terms]) AND (Filters: Publication date from 1980/01/01 to 2015/12/30)

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 Cochran'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

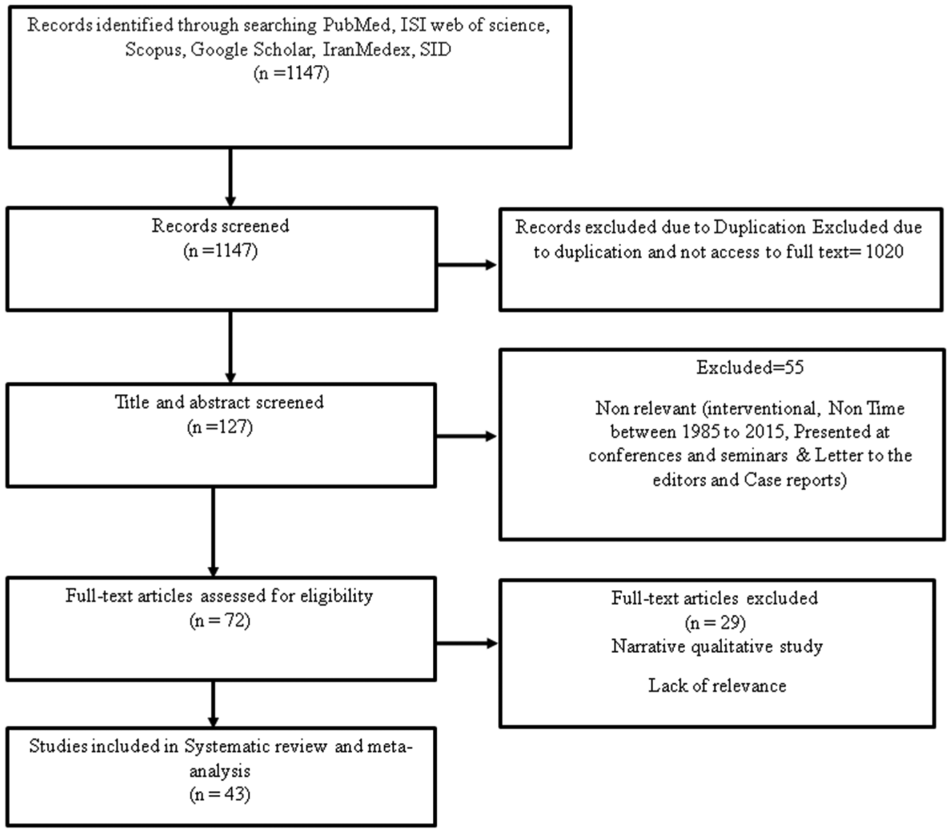

Figure 2: Flow diagram for study selection progress

assessment. The search strategy was presented in Table 1. Finally, after full-text assessment, 43 articles (abstract with full-text articles) which described the prevalence of rotavirus in Iran were selected for analysis and are presented in Table 2. In these studies, we investigated samples include rotavirus infectious specimens that had taken from patients with different gender and age. It is notable that most of the studies were conducted in central and north parts of Iran, followed by south.

Using random-effect models, the pooled prevalence of rotavirus was estimated 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 $I^2 = 98.7\%$). 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 1986–19991 was 20%, 1990–2004 was 29%, and in 2001–2008 was 40%.[8] 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%.[8] 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%).[54] Rotavirus infection rate was 20%–30% in some Asian countries including Hong Kong, India, Bangladesh, and South Korea, but it was

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 aggulutation	NR	[21]
Kazemi	2006	Isfahan	185	30.8	Stool	ELISA	NR	[22]
Zarnani	2004	Tehran	704	15.3	Stool	ELISA	NR	[23]
Samarbafzadeh	2005	Ahwaz	137	26.2	Stool	dsRNA-PAGE	NR	[24]
Samarbafzadeh	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	[28]
Savadkoohi	2007	Babol	208	60.5	Stool	ELISA	NR	[29]
Kargar	2012	Shiraz	138	34.7	Stool	ELISA	NR	[30]
Emamghorashi	2015	Jahrom	102	67.6	Stool	ELISA, latex agglutination	NR	[31]
Farahtaj	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	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

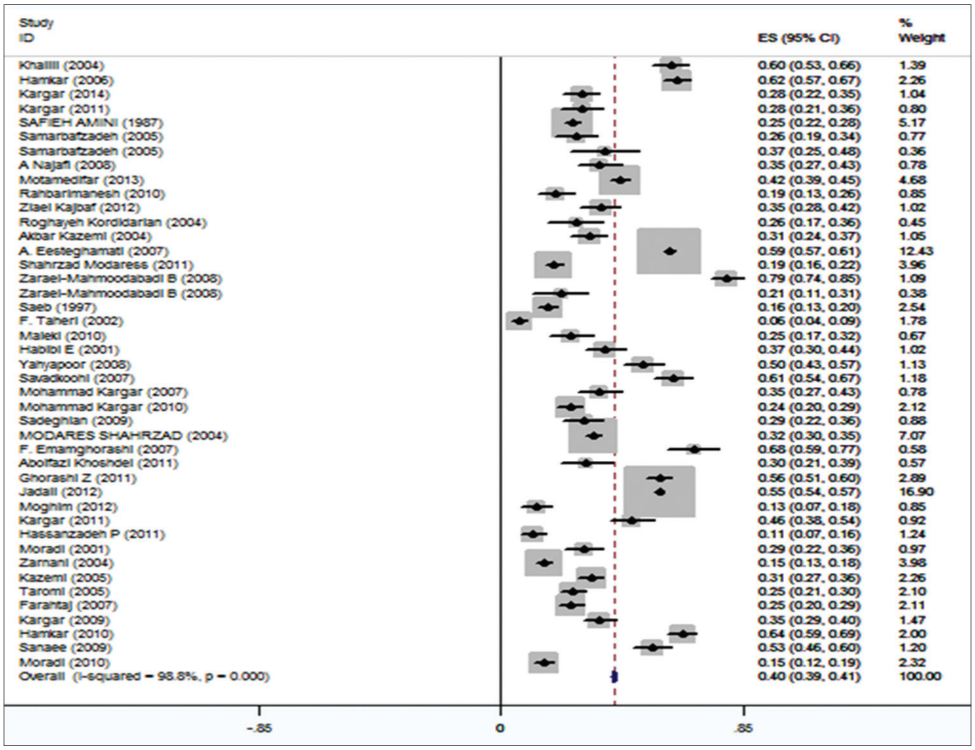

Figure 3: Results of meta-analysis for pooled prevalence with 95% confidence interval and its forest plot

43%–58% in China, Vietnam, Japan, Taiwan, Myanmar, and Thailand.[55] Latipov *et al.* showed rotavirus positivity in Central Asia region (2011) including Kazakhstan (15%), Uzbekistan (49%), and Kyrgyzstan (36%).[56] In the study carried out by Akan *et al*. (2009) in Turkey, the prevalence of rotavirus was 18.7%.[6] In another study by Podkolzin *et al.* carried out in Russia, the rotavirus proportion was 44%.[57] Various recent studies showed the proportion of rotavirus infection in Latin America (30%), Europe (40%), and Africa and Middle East (34%–40%).[58-61] Bwogi *et al.* detected rotavirus in 37% (263/712) of the children in Uganda (2012–2013).[62] 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).[59] 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.[7,34] 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.[54] 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.[36] 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 seen.[63] 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.[63] 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.[64,65] 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.

Acknowledgment

We are greatly thankful to the director and principal of Iran University of Medical Sciences for their constant encouragement and support of research for this study. We are also thankful to all the faculty members of "Virology" and "Epidemiology and Biostatistics" Department for technical assistance in research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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