Rotavirus Infection in Children with Acute Gastroenteritis in Iran: A Systematic Review and Meta-analysis

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ABSTRACT

Background: The recent studies show that *Rotavirus* is important cause of the acute gastroenteritis. The aim of this review is to estimate the number of *Rotavirus* infection among Iranian children by performing a systematic review and estimating a pooled data.

Methods: We performed a systematic literature review in relevant databases including PUBMED, MEDLINE, OVID, SID, MAGIRAN, and IRANMEDEX. Search in databases was done in October 10, 2013. Meta-analysis was performed using the STATA statistical package version 11. We assessed heterogeneity by Q-test and used random model for pooling measures of proportion of *Rotavirus* infection among Iranian children with diarrhea (and 95% confidence intervals [CI]). Sub group analysis between in-patient and outpatient group were done and publication bias was assessed by Egger and Begg tests.

Results: A total of 154 records were identified in our searching. There were 36 studies including a total of 15,368 children with diarrhea. Out of 15,368 children, 6,338 were positive for *Rotavirus* gastroenteritis. Overall pooled estimate of infection with *Rotavirus* among cases of gastroenteritis was 0.35 (95% CI, 0.28-0.41). Pooled estimates for hospitalized children and outpatient subgroups were 0.39 (95% CI, 0.30-0.48), and 0.31 (95% CI, 0.23-0.38), respectively.

Conclusions: This study supports the importance of *Rotavirus* in the Iranian population such as common cause of diarrhea among children. Therefore, decision to adopt immunization programs to prevent *Rotavirus* infection might be helpful in Iran.

Keywords: Acute gastroenteritis, children, and diarrhea, *Rotavirus* infection

Review Article

INTRODUCTION

Acute diarrhea can be particularly detrimental to children, every day killing 2200 infants and children worldwide.[1] *Rotavirus* infection among uner-5-year-old children is a common cause of childhood gastroenteritis, especially in those countries which has

not launched a *Rotavirus* vaccination program. The initial symptoms associated with *Rotavirus* infection include watery diarrhea and vomiting, which sometimes aggravates resulting in severe dehydration requiring hospitalization. Every child encounters at least one episode of *Rotavirus* gastroenteritis by the age of 5 years. Each year, about 2 million subjects have to be hospitalized for developing severe *Rotavirus* gastroenteritis while about 25 million patients seek medical help by visiting a physician's office or clinic and 111 million cases require care at home.[2,3] *Rotavirus* infection also causes 527000 deaths annually among children up to 5 years of age worldwide and most of these deaths occur in the developing countries.[4] *Rotavirus* can be detected in high concentrations in the stool of children suffering from gastroenteritis (1012 viruses/gram). Control measures such as improved sanitation is not effective in preventing this disease.[5,6] Several studies performed in the Middle East showed that approximately 40% of hospitalized patients suffering from gastroenteritis were infected with *Rotavirus*.[2,7] In Iran, data collected from different geographical regions revealed that the proportion of *Rotavirus* infection among children with gastroenteritis ranges from 11.6% to 64.67%.[8,9] The emergence of two *Rotavirus* vaccines (Rotarix® by Glaxo Smith Kline and RotaTeq® by Merck) have markedly reduced the morbidity and mortality associated with severe *Rotavirus* diarrhea. Therefore, at present, the vaccination strategy to prevent *Rotavirus* infection has gained tremendous importance. The implementation of universal vaccination program worldwide can decrease the medical and other costs associated with the hospital stay and clinic visits,[10,11] however the epidemiology of *Rotavirus* is an important element for making decision for such vaccination.

Although, several studies related to *Rotavirus* infection have been conducted in Iran, precise data for making accurate prediction of the benefits associated with a preventive program required for policy making is not available. The primary aim of this study was to perform a systematic review and meta-analysis on the data published from previous studies in order to calculate pooled estimates of *Rotavirus* gastroenteritis magnitude (incidence in general population of children and/or proportion of infection in cases with gastroenteritis who admitted to hospitals or visited in the outpatient clinics.

METHODS

We performed a systematic review and meta-analysis of observational studies of *Rotavirus*, according to the (Meta-analysis Of Observational Studies in Epidemiology) guidelines.[12] Different phases of the study included searching, screening, selecting of studies, extracting data, data cleaning and analyzing.

Search strategy

To retrieve related studies, we used a sensitive librarian-assisted search strategy (follicle stimulating hormone) in relevant databases including, PubMed Medline, Ovid, SID (Scientific information Database), Magiran and Iranmedex since 1/1/1997 onward, in which reported indicators of *Rotavirus* magnitude were targeted. The last round of search in databases was performed in October 10; 2013. We used sensitive search queries to avoid unwanted loss of information. The following search strategy was developed for MEDLINE via Ovid SP and then adapted to the other resources:

("*Rotavirus* Infections/epidemiology" OR "Gastroenteritis/epidemiology" OR "Diarrhea/epidemiology" AND Iran AND ("humans" AND "infant" OR "infant, newborn" OR "infant" OR "child, preschool"[MeSH Terms]).

We did not limit our search to a certain language or time period to avoid missing possible related works. In addition, we did a manual reference checking and citation tracking of related papers thorough Thomson Reuters' Web of Science, Elsevier's Scopus and Google Scholar.

Inclusion criteria

In this review, cross-sectional or longitudinal studies involving children up to 6 years of age have been included. The infection with *Rotavirus* in these children were assessed by one of the acceptable laboratory diagnostic tests including the enzyme immunoassay (EIA), rapid test, latex agglutination (LA) test or polyacrylamide gel electrophoresis (PAGE).

Exclusion criteria

Laboratory studies conducted on animals were excluded. Furthermore, studies using nonstandardized methods or clinical outcomes without laboratory confirmation were excluded from this study.

Study selection

Full-texts of the relevant studies were critically appraised for eligibility criteria by two researchers independently (SSH and MML). Unrelated and duplicated articles were excluded based on title and abstract. Flow diagram of articles included in the systematic review is shown in Figure 1.

Data extraction

Data extraction was carried out by two researchers (SSH and MML). Bibliographic data, background data (such as sample characteristics), methodological data and epidemiologic data were collected. As the epidemiologic data, we collected nominators and denominators and reported confidence intervals (CI).

Quality assessment

The quality of articles was assessed by the researchers with a checklist of STROBE (Strengthening the Reporting of Observational studies in Epidemiology).[13] The majority of studies selected for this review had been assessed to be of moderate to good quality, but articles thought to be of lower quality were not excluded. The quality of the studies documented in the articles was assessed primarily based on the techniques used for detecting *Rotavirus* in the reported proportion of gastroenteritis.

Data synthesis

We collected and cleaned data in a Microsoft excel sheet. The data then transferred to statistical package; Meta-analysis was performed using the STATA statistical package version 11. First, we assessed heterogeneity based on the presence of at least one of these two criteria: *P* value for Cochran's Q-test < 0.1 or Higgins' I2 statistic of more than 50%. We used random or fixed model for pooling measures of proportion of *Rotavirus* infection in case of heterogeneous and homogenous studies, respectively. All pooled estimates were reported with 95% CI. Subgroups were determined based on health care utilization type (inpatient and

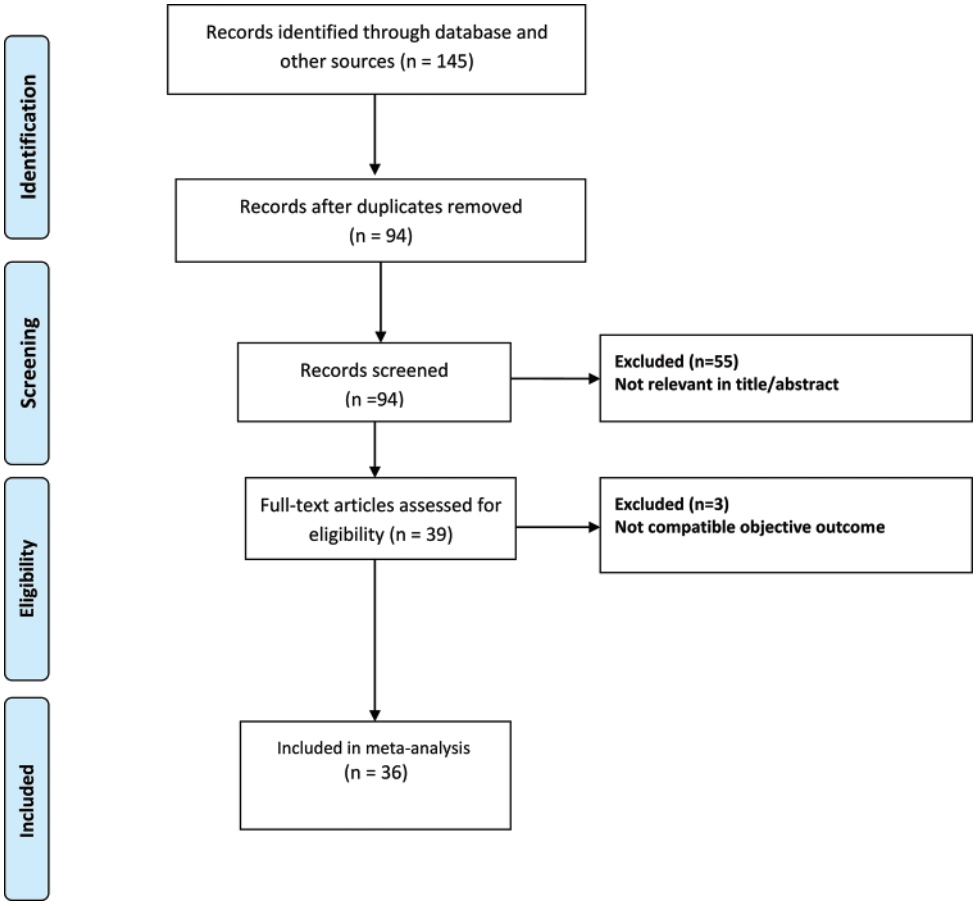

Figure 1: Flow chart of the selection process records

outpatient). Potential publication bias was assessed by Egger regression asymmetry test and Begg adjusted rank correlation test.

RESULTS

Study selection

The electronic searching identified 132 studies from databases and we found 13 other studies by manual searching. Out of these 145 studies, 51 studies were duplicates. After screening of titles and abstracts, 54 studies were excluded from the analysis. The full-texts of 39 relevant articles were checked for eligibility criteria after investigating the full reports, and consequently, 3 studies were excluded. Finally, 36 studies with a total number of 15368 participants were evaluated the proportion of infection with *Rotavirus* in cases of gastroenteritis [Figure 1]. We found no report about the incidence of Rotaviral infection among healthy children.

Out of total 36 studies selected for this review, 15 studies were conducted in children in outpatient settings[8,9,14-28] and 21 studies involved inpatient cases.[8,18-19,29-47] Furthermore, three studies involved both inpatient and outpatient settings[8,18,19] A number of studies conducted in the same setting bear similar number and date.

A total of 15,368 children up to 6 years of age were diagnosed with symptoms of acute gastroenteritis, and out of them, the stool samples of 5,884 children were positive for *Rotavirus*. Out of 15,368 children, 11,371 and 3,997 children were treated in hospitals (inpatient population) and outpatient settings, respectively. Among these cases, 5,166 children of the inpatient population and 1,172 children of the outpatient population were positive for *Rotavirus*. The range of *Rotavirus* infection proportions were between 11.36%[8] and 79.0%.[9] The median of *Rotavirus* positive cases was estimated 0.33 for all studies which was 0.35 and 0.26 for inpatient and outpatient, respectively. The trend showing the median proportion of *Rotavirus* infection over the calendar time is depicted in [Figure 2]. High proportion of *Rotavirus* infection was observed form 2006 to 2009 for children in the inpatient setting while similar trend was reported for outpatient setting from 2009 to 2010.

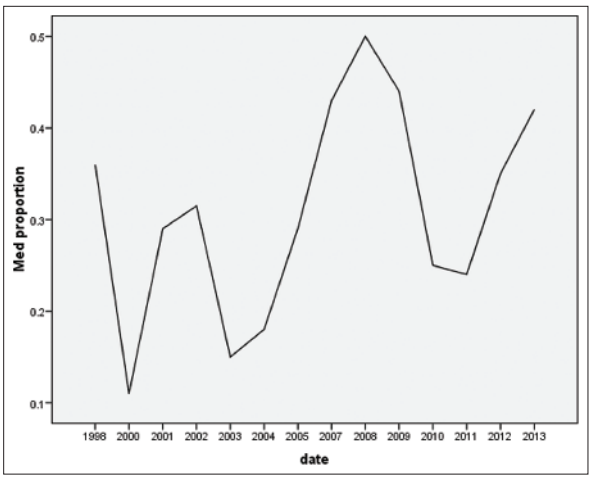

Figure 2: Median proportion *Rotavirus* gastroenteritis in over time of the study

Our findings showed that there was moderate heterogeneity among these studies (I2 = 50%, Moment-based estimate of between studies variance = 0.03). As a result, statistical analysis was done by random effect model with 95% CI, also subgroup analysis was performed. The results of Meta-analysis using a random effect model revealed an estimate of 0.36 (95% CI: 0.30-0.42) [Figure 3] pooled estimate for inpatient and outpatient population was 0.39 (95% CI: 0.30-0.48) [Figure 4] and 0.31 (95% CI: 0.23-0.38) respectively [Figure 5].

Publication bias for proportion of cases with *Rotavirus* was assessed by Eager and Begg test that were not significant. *P* values for Begg and Egger test were 0.238 and 0.894 respectively.

Seasonal and geographical distribution is demonstrated in Table 1 27 studies have reported seasonal prevalence among which the highest rate of prevalence was found in cold and hot seasons in 21 studies and 6 studies respectively. In addition, the highest prevalence was found in children <2 years.

In order to minimize bias we use lab test with high sensitivity and specificity for diagnosis virus such as ELISA, PAGE of *Rotavirus* double-stranded RNA and LA test. Studies using less sensitive methods such as chromatography were excluding from review. 26 studies have used ELISA and EIA method to diagnose the virus [Table 1]. Most studies did not report genotype of the virus, genotype was identified in 13 studies and most frequent genotypes were G1 and G4.

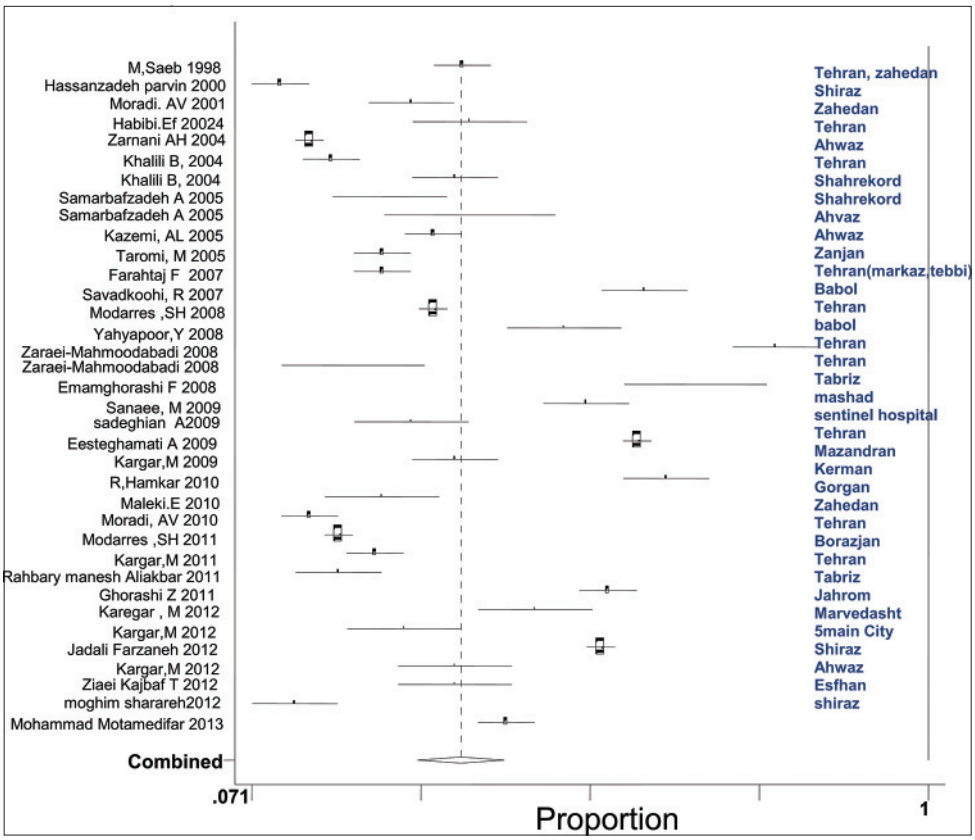

Figure 3: Forest plot of the studies overall combined effects proportion *Rotavirus* infection in the Iranian children with gastroenteritis for total studies

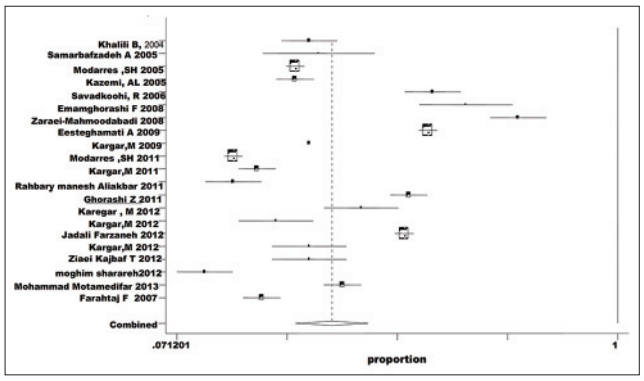

Figure 4: Forest plot of the studies, combined effects proportion rate *Rotavirus* infection in the hospitalized Iranian children with gastroenteritis

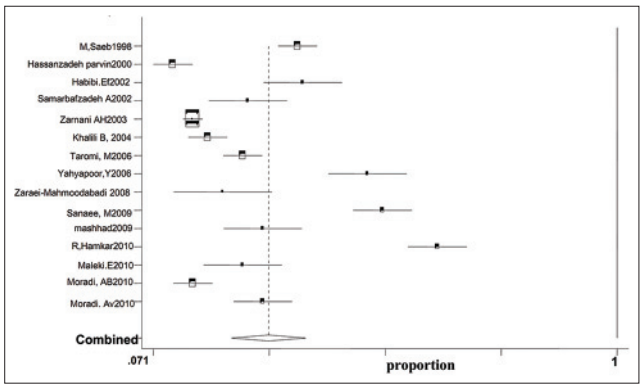

Figure 5: Forest plot of the studies, combined effects proportion *Rotavirus* infection in the community based Iranian children with gastroenteritis

DISCUSSION

According to our study results, the overall proportion of *Rotavirus* infection among cases of gastroenteritis was 0.36 (95% CI, 0.30-0.42). In addition, this study investigated *Rotavirus* gastroenteritis occurrences covering a wide region in the country, and the estimated proportion of infection varied from 11.36% in Shiraz to 67.64% in Mazandaran and 79% in Tehran.[8-9,30] There are several variables in these studies that might explain the variance such as different geographical locations, different time periods and seasons, different methods of virus detection, age group, and gender. Furthermore, the proportion can be influenced by the control level of other pathogens of diarrheal diseases. High-percentage of *Rotavirus*

Table 1: Details of the studies included in the meta-analysis

Date	Name date	Study location	Seasonal prevalence	Lab test	Genotyping	N pop	Cases	Proportion	95% CI	References
1998	Saeb	Tehran, Zahedan	NR	ELISA	NR*	450	160	0.36	0.32-0.4	[14]
2000	Hassanzadeh	Shiraz	Aban, ordibehesht	Culture, electeronic microscopic	NR	220	25	0.11	0.07-0.15	[9]
2001	Moradi	Zahedan	Warm	ELISA	NR	171	50	0.29	0.23-0.35	[15]
2004	Habibi	Tehran	Cold	ELISA	G1, G4	180	66	0.37	0.29-0.45	[16]
2004	Zarnani	Tehran	Spring	EIA	NR	704	108	0.15	0.13-0.17	[17]
2004	Khalili	Shahrekord	Cold	ELISA	G1p8	245	45	0.18	0.14-0.22	[19]
2004	Khalili	Shahrekord	Cold	ELISA	G1p8	259	91	0.35	0.29-0.41	[19]
2005	Samarbafzadeh	Ahwaz	NR	dsRNA PAGE	NR	137	36	0.26	0.18-0.34	[18]
2005	Samarbafzadeh	Ahwaz	NR	dsRNA PAGE	NR	63	23	0.37	0.25-0.49	[18]
2005	Kazemi	Zanjan	Cold (paeez)	ELISA	NR	400	126	0.32	0.28-0.36	[30]
2005	Taromi	Tehran (Markaz Tebbi)	Cold	ELISA	G1	372	94	0.25	0.21-0.29	[20]
2007	Savadkoohi	Babol	Cold	EIA	NR	208	126	0.61	0.21-0.29	[21]
2007	Farahtaj	Tehran	NR	ELISA	G1P8	374	92	0.25	0.55-0.67	[22]
2008	Yahyapoor	Babol	NR	EIA	NR	200	100	0.50	0.3-0.34	[23]
2008	Emamghorashi	jahrom	NR	ELISA	NR	102	69	0.68	0.42-0.58	[31]
2009	Kargar	Tehran		ELISA	NR	260	90	0.35	0.73-0.85	[35]
2008	Modarres	Tehran	Cold	dsRNA PAGE	NR	1250	404	0.32	0.11-0.31	[29]
2010	Hamkar	Mazandran	Cold	EIA	NR	353	225	0.64	0.58-0.78	[24]
2008	Zaraei-Mahmoodabadi	Tehran	Cold	ELISA	NR	193	153	0.79	0.47-0.59	[8]
2008	Zaraei-Mahmoodabadi	Tehran	Cold	ELISA	NR	67	14	0.21	0.21-0.37	[8]
2009	Eesteghamati	Sentinel Hospital	Cold	EIA	G4p, G1	2198	1298	0.6	0.58-0.62	[32]
2009	Sanaee 2009	Tabriz	Cold	ELISA	G4, G1	213	113	0.53	0.29-0.41	[33]
2009	Sadeghian	Mashhad	Summer, winter	Latex agglutination test	NR	156	45	0.29	0.58-0.7	[34]
2010	Maleki	Kerman	NR	SDS-PAGE	NR	118	29	0.25	0.17-0.33	[35]
2010	Moradi	Gorgan	Cold	SDS-PAGE	NR	411	62	0.15	0.11-0.19	[36]
2011	Modarres	Tehran	NR	dsRNA PAGE	G1p8	700	131	0.19	0.17-0.21	[40,36]
2011	Kargar	Borazjan	Cold	ELISA	G1, G4	375	91	0.24	0.2-0.28	[38,45]
2011	Rahbary manesh	Tehran	NR	dsRNA-PAGE	G1p8, G4	150	29	0.19	0.13-0.25	[41]
2011	Ghorashi	Northwest (Tabrize)	Cold	EIA	NR	511	284	0.56	0.52-0.6	[42]
2011	Karegar	Jahrom	Cold	EIA	G1, G4	163	75	0.46	0.38-0.54	[37,39]
2012	Kargar	Marvedasht	Warm	ELISA	mix, G2, G4	141	40	0.28	0.2-0.36	[34,47]
2012	Jadali	5 main city	Cold	ELISA	NR	2988	1658	0.55	0.53-0.57	[43]
2012	Kargar	Shiraz	Cold	EIA	G4, G1	138	48	0.35	0.27-0.43	[33,49]
2012	Ziaei Kajbaf	Ahvaz	Cold	ELISA	NR	180	63	0.35	0.27-0.43	[48]
2012	Moghim	Esfhan	Warm	dsRNA electrophoretypes	NR	150	19	0.13	0.07-0.19	[44]

Contd...

Table 1: Contd...

Date	Name date	Study location	Seasonal prevalence	Lab test	Genotyping	N pop	Cases	Proportion	95% CI	References
2013	Motamedifar	Shiraz	Summer, fall	EIA	NR	827	347	0.42	0.38-0.46	[50]

PAGE=Polyacrylamide gel electrophoresis, EIA=Enzyme immunoassay, dsRNA=Double-stranded RNA, SDS=Separate Double-Stranded, NR=Not Reported, CI=Confidence interval

in some provinces might be simply the result of better control of other pathogens. Unfortunately, we did not find useful information for calculating the incidence of Rotaviral diarrhea. In addition, most of these studies have not incorporated enough findings based on molecular epidemiology and the most commonly used method for virus detection has been EIA, ELIZA.

Using ELIZA and EIA method with high sensitivity and specificity leads to reduction bias in virus detection in 76% of studies (26 studies).[51-52] Molecular analysis was performed in 13 studies in which most common types (G1 and G4) have been reported. These types are more similar to the identified types in Europe. Epidemiological surveys in the Mediterranean countries have been variable, and so that increase in a particular genotype has not been found in this area. For instance, G1 has increased in Turkey as well as Iran, but G4 has decreased, on the other hand in Saudi Arabia G2 has increased.[2] Molecular identification of virus types is an important component of incidence and prevalence studies, because it has been considered as a strategy to select type of vaccine. There were no facilities for molecular identification of the virus in this review. Furthermore, the included studies were not designed to do so, well designed epidemiological study in order to investigate the type of the virus seems necessary.

Among 75% of studies in which reported seasonal outbreak, 21 studies have shown an increased prevalence of disease in the cold season. Seasonal prevalence is higher in cold seasons in some countries such as Tunisia, Pakistan and Saudi Arabia and in hot season in Jordan. According to Malek *et al.*, Iran and Egypt does not follow any seasonal trend, but in this review it was demonstrated that most infections occur in the cold season in Iran.[7]

In many cases concurrent infection with *Rotavirus* included Adenovirus, Astrovirus and some enteric pathogen have been seen that need to correct the approach for diagnostic and treatment.[53]

Four studies have mentioned co-infection with Adenovirus and Astrovirus[25,32,48,50] Ziaei Kajbaf *et al.*, showed that most cases of co-infection with Adenovirus were at 7-12 months and seasonal peak of diseases has been reported in the fall.[48] Co-infection with adenovirus was seen in another study in Shiraz, specific in 24-59 months. Although co-infection rate has reached 29%in some months, *Rotavirus* infection was higher at all of age.[50] In two studies conducted in Mazandaran, concurrent infection with Adenovirus and Astrovirus were also noted.[21,23]

Many epidemiologic studies have been performed worldwide. In 2010, Malek *et al.*[7] conducted a review study featuring 20 countries in the Eastern Mediterranean Region (EMR). The median proportion rate of *Rotavirus* diarrhea in hospitalized children with acute gastroenteritis infection was determined to be 40% (99% CI, 17-46%). The same proportion rate in an outpatient setting was calculated to be 23% (99% CI, 6-41%). Although this review included just one study from Iran in the inpatient category and two studies in the outpatient setting, a high degree of heterogeneity was observed. Findings from recent studies conducted in the EMR by "WHO" indicated that the mortality rate associated with *Rotavirus* disease and the burden of developing severe *Rotavirus* infection remain high, in countries with the lowest per capita income, such as Pakistan, Afghanistan, Sudan, Yemen, and Somalia. Countries with higher per capita income have fewer deaths reported from *Rotavirus* diarrhea. Overall, severe *Rotavirus* disease among children under 5 years is prevalent in the EMR resulting in higher economic costs.[2]

In another study covering the Middle East Region, Khoury *et al.*[2] determined the overall percentage of *Rotavirus* detection among gastroenteritis cases ranging from 16% to 61%.[7] This report showed that the overall detection of *Rotavirus* in gastroenteritis episodes was lowest

in countries such as Saudi Arabia, Tunisia and Egypt (16-23%) and countries with higher detection of *Rotavirus* infection included Syria (61%) and Oman (51%).[7] The overall annual detection of *Rotavirus* gastroenteritis reported by WHO in the EMR was 42%, and this included Egypt, Iran, Iraq, Jordan, Libya, Morocco, Oman, Syria, Tunisia and Yemen.[7]

The estimated range (30-42%) derived from our study is similar to the results observed in some of the Middle East countries such as Iraq, Jordan, and Morocco. Furthermore, Khoury *et al.*[2] showed that in Iran and Egypt, the proportion of *Rotavirus* gastroenteritis have increased over time (15% in 2003-2004 vs. 59% in 2005-2006). However, in this review only two studies were included from Iran. The mentioned figure is not completely compatible with our results (from 36 different studies) [Figure 2].

One of the limitations associated with the present study is the lack of adequate data because of limited access to databases. As illustrated in [Figure 2], the proportion of *Rotavirus* detection in cases with gastroenteritis increased over time from 2006 to 2010, although, the median proportion rate of *Rotavirus* infection did not show any specific trend with respect to time. We did not stratified results based on age, gender and virus genotype and this shortcoming was mainly due to lack of adequate information on these factors in most of the articles used for this review. However, findings from a study conducted in the regions of Mazandaran, Zahedan, Gorgan and Babol indicated that in children <2 years of age are a higher proportion of *Rotavirus* infection especially in the cold season.

Another important factor that can cause underestimation of *Rotavirus* infection is the display of symptoms. *Rotavirus* associated diarrhea was the ubiquitous symptom reported among children admitted to clinics or hospitals, other symptoms of gastroenteritis such as vomiting or abdominal pain without diarrhea were hardly reported. Phillips *et al.*[54] indicated that the prevalence of asymptomatic *Rotavirus* infection was 11% from the general population of England. In addition, Abiodun *et al.*[55] showed that the incidence of asymptomatic *Rotavirus* infection was 19.1% and 15.1% in boys and girls respectively in Nigeria.

In our review, *Rotavirus* infection in 86% of cases was higher in boys than girls.

Conducting virus detection tests for all the associated symptoms of gastroenteritis might change *Rotavirus* infection particularly in community-based studies. In addition, the lack of reliable epidemiologic data involving nosocomial and home care cases can also affect our estimated proportion. Information obtained from worldwide reports indicated that nearly 111 million cases of *Rotavirus* gastroenteritis were treated at home only.[2] In cases of limited access, the proportion of people who do not seek care from an outpatient or inpatient facility will be higher. The care seeking behavior is not influenced balanced for all pathogens, because of the difference in severity of symptoms.

CONCLUSIONS

The present review showed the importance of *Rotavirus* in children with diarrhea in Iran. Among the various pathogens causing gastroenteritis, *Rotaviruses* leads to the most severe form of acute gastroenteritis among children <6 year of age.[56] Preventive measures such as improved sanitation are not sufficient to combat *Rotavirus* transmission.

Based on the IrMIDHS, 13.5% of under-5-year-old children had experiences diarrheal diseases within 2 weeks before the survey, and 59.5% were visited in an outpatient or inpatient facility.[57] Although, *Rotavirus* might not be the causal pathogen in all children with laboratory proven *Rotavirus* infection, it certainly has important quota among total cases of diarrhea. To be more useful, the present study should be completed by prevalence of *Rotavirus* in the general population of asymptomatic children. We think the results of this study can be used in combination with other evidences for making decision regarding the introduction of the vaccine against *Rotavirus*.

Since, once infected with *Rotavirus* does not provide permanent safety, implementing vaccination program against *Rotavirus* not only could be averted *Rotavirus* infection disease, but also it could be saved medical and social cost. Performing cost effectiveness study and the priority setting investigation seem necessary. Due to variety type of vaccine could be effected certain genotype, high level evidence should be determined in order to make a decision about certain type of vaccination.

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