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Research Article

Epidemiology of Norovirus Infections Among Acute Gastroenteritis Patients in the Middle East and North Africa Region, 2010-2018

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Abstract

Norovirus (NoV) is well recognized as a leading cause of acute gastroenteritis across all age groups, worldwide. This study aimed to assess the prevalence of human norovirus across all ages with gastroenteritis and distribution of NoV genotypes in the Middle East and North Africa region. We retrieved 46 articles/abstracts of human norovirus in the Middle East and North Africa between 2010 and 2018 then we selected 32 articles/abstracts that met our predefined inclusion criteria and were used to extract full data. The mean overall prevalence of NoV was 11.8% (rang 1.8-36.8%) in patients with gastroenteritis. NoV GII.4 was the predominant serotype detected in most of the selected studies that presented genotyping data. GII.3 was the second most detected genotype among patients. NoV gastroenteritis was detected all year round with a peak incidence observed during the winter and autumn seasons. The majority of NoV infection was reported in males than females, who younger than 2 years of age. In conclusion, human NoV is a common pathogen of diarrhoea in children in the Middle East and North Africa. However, there is little data on NoV infections in adults. This study provides a valuable data on norovirus epidemiology required for future vaccine policy decisions.

Keywords: Norovirus; Middle East and North Africa; Children; Acute Gastroenteritis; Seasonality

Introduction

Acute gastroenteritis (AGE) is a primary cause of global morbidity and mortality [1,2]. AGE is the second most-common infectious disease, causing about 1.45 million deaths each year worldwide [2]. Norovirus (NoV), belonging to Caliciviridae family, is now well-identified as the leading cause of global AGE [3]. NoV genome contains three open reading frames (ORFs). ORF-1 encodes non-structural proteins (RNA-dependent RNA polymerase); ORF-2 encodes a capsid protein (VP1); and ORF-3 encodes a minor capsid protein (VP2). Based on differences in the nucleotide sequence of VP1, NoV are currently classified into seven genogroups, NoV GI- NoV GVII, but only genogroups NoV GI, GII, and GIV are associated with human AGE [4]. Of these, NoV GI is subdivided into 9 genotypes, whereas GII consists of 23 genotypes [5]. NoV GII is recognized to have a wider distribution than that of NoV GI, playing a big role in AGE globally [6]. The faecal-oral mode is the primary transmission rout, followed by other routes, such as transmission via vomitus, water, food, water, person-to-person, environmental contamination [7-12]. The first outbreak of a NoV-AGE was reported in the United States in 1968. After that, NoV-AGE has become epidemic across all age groups in both developed and developing countries [8,12]. NoV is responsible for about 19-21 million illnesses, 400,000 emergency department visits, 1.7-1.9 million outpatient visits, 56,000-71,000 hospitalizations, and 570-800 deaths per year in the United States alone [13].

NoV infection is often self-limiting in healthy adults, requiring only supportive therapy and rehydration; however, disease can be severe and even fatal in the young children and elderly [14]. Furthermore, NoV infection can be chronic in immunocompromised hosts [14], solid organ transplant patients [15], especially in patients who undergo kidney [17], heart transplants [18], or pancreas [19]. Thus, it is great important to understand the epidemiology of NoV AGE so the aim of this review was to summarize the NoV prevalence and genotype distribution in the Middle East and North Africa.

Materials and Methods

Search strategy

This systematic literature search was performed on articles studying NoV gastroenteritis in the 18 countries of the North Africa and the Middle East (Algeria, Bahrain, Egypt, Iran, Iraq,

Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, UAE and Yemen) during the past 10 years (2010-2018). Articles were collected from three electronic websites: google scholar, PubMed, science direct, with the keyword "noroviruses and Norwalk". After reviewing the collected article, studies/abstracts were selected if they met the following inclusion criteria 1) Studies for the detection of Human NoV and Norwalk virus in patients with gastroenteritis; 2) Studies published in the countries of the North Africa and Middle East between 2010 and 2018; 3) Studies used standardised laboratory methods for detection/genotyping of NoV including ELISA, EIA, RT-PCR, Real time RT-PCR, and sequencing.

Results

We reviewed 46 articles/abstracts published during 2010 - 2018 to select only 32 studies that met the inclusion criteria of the current research. The selected studies covered Egypt [20-23], Islamic Republic of Iran [24-30], Iraq [31-35], Jordan [36], Kuwait [37,38], Lebanon [39,40], Libya [41], Morocco [42], Qatar [43], Tunisia [44-46], Turkey [47-50], Yemen [51]. The included studies in the current research contained the following topics: prevalence of NoV gastroenteritis (n = 32), seasonal variation (n = 14), age distribution (n = 18), gender distribution (n = 14), genotype distribution (n = 20), and disease severity (n = 14 articles). Several countries (Algeria, Bahrain, Oman, Palestine, Saudi Arabia, Syrian Arab Republic, and United Arab Emirates) were not were not included in this review due to absence of studies related to norovirus gastroenteritis. However, very low articles were found in several countries (Jordan, Kuwait, Lebanon, Libya, Morocco, Qatar, and Yemen) but the majority of studies (23/32) came from only five countries (Egypt, Iran, Iraq, Tunisia, and Turkey), as presented in Table 1.

Prevalence of NoV gastroenteritis

Specimens from 12430 from patients (hospitalized and/or outpatients) with acute gastroenteritis in 12 countries were tested for NoV as part of 32 studies. The majority of studies (15/32) used RT-PCR as the sole detection technique [21,26,29,31,32,36 ,40,44,45,47,49], four used real time RT-PCR [30,41,43,46], four used immunochromatography assay (IC), three used enzyme immunoassays (EIA) [20,27,39], and one used enzyme-linked immunosorbent assay (ELISA) [33]. The remaining five studies used a combination of methods. The pooled detection rate of human NoV in all studies was 11.8% (1456/12430) where the prevalence rates of NoV was ranged from 1.8% to 36.8% (Table 2). The highest detection rate (≥ 30%) of NoV infection was found in studies from Egypt [23], Iran [28], Iraq [32], and Tunisia [46]. The lowest detection rates were reported in two studies from Iran and Kuwait with 4.1% and 1.8%, respectively [26,38]. When we combined and pooled studies of each country, the highest detection rate of NoV infections was found in Qatar (28.4%) and Iraq (19.3%) whereas the lowest detection rate was found in Iran (7.3%) and Kuwait (8.9%), as shown in figure 1.

Seasonal distribution of NoV gastroenteritis

Twenty published studies from 8 countries reported seasonality distribution including Egypt [20,23], Iran [25,27,29], Iraq [31], Libya [41], Morocco [42], Qatar [43], Tunisia [45,46], Turkey [48]. Most of these studies [23,25,27,29,31,45,46,48] reported that the peak incidence NoV gastroenteritis is in the winter and autumn. Few studies [20,41,42,43] reported that the peak incidence of noroviral infection is in summer as presented in Table 2.

Table 1: Literatures of extracted data by country.

Country	Prevalence of NoV	Seasonality	Age distribution	Gender distribution	Clinical features	Genotyping
Egypt	[20-23]	[20,23]	[20,22,23]	-	[21,23]	[21]
Iran	[24-30]	[25,27,29]	[25,27,29,30]	[25,27-30]	[24,25,27]	[24,25,29,30]
Iraq	[31-35]	[31]	[31,33]	[31,33]	[31]	[32,33]
Jordan	[36]	-	[36]	-	-	[36]
Kuwait	[37,38]	-	[37]	[37]	-	[37]
Lebanon	[39,40]	-	[40]	[39,40]	[39,40]	[39,40]
Libya	[41]	[41]	[41]	-	[41]	[41]
Morocco	[42]	[42]	[42]	[42]	[42]	[42]
Qatar	[43]	[43]	[43]	-	-	-
Tunisia	[44-46]	[45,46]	[44]	[44,45]	[45]	[44,45,56]
Turkey	[47-50]	[48]	[48,50]	-	[48,49]	[47,49,50]
Yemen	[51]	-	-	[51]	[51]	[51]

Country	Ref.	Study characteristics				Study results				
		Year(s) of Sample collection	Duration of sample collection per month	Age, years	Method	No. of samples	Prevalence No (%)	Peak Season	Peak Age per month	Peak gender M/F
Egypt	[20]	2005-2007	-	< 5	EIA	2,112	191(9%)	Warm	0-12	-
	[21]+	-	-	< 3	RT-PCR	86	22(25.58 %)	-	-	-
	[22]*	2012-2013	12	< 15	RT-PCR	500	61(16.2)%	-	12-36	-
	[23]*	2015-2017	24	< 5	RT-PCR	100	30(30%)	Winter	12-24	-
Iran	[24]	2008-2009	12	< 85	RT-PCR	293	29(9.8)%	-	-	-
	[25]	2008-2009	-	< 5	RT-PCR	143	9 (6.29%)	winter	36-60	M
	[26]	NM	-	< 5	RT-PCR	2,170	90 (4.14%)	-	-	
	[27]	2008-2010	24	< 7	EIA	375	47(12.35%)	Autumn	12-17	M
	[28]	2013	3	< 12	IC	82	27(32.92%)	-	-	M
	[29]	2013-2014	12	< 5	RT-PCR	170	15 (8.8%)	Autumn	13-24	M
	[30]	2015-2016	12	< 5	qRT-PCR	210	36 (17.1%)	-	7-12	M
IRAQ	[31]	2011-2012	12	< 5	RT-PCR	192	16(8%)	Winter and autumn	18-23	M
	[32]	2012-2013	12	< 5	RT-PCR	152	81 (32.27%)	-	-	-
	[33]	2014-2015	6	< 14	ELISA	100	28(28%)	-	24-60	M
	[34]	2016-2017	4	< 8	IC	200	8(27.6%)	-	-	-
	[35]	2017	5	< 15	IC	160	22(13.75%)	-	-	-
Jordan	[36]	2006-2007	24	< 5	RT-PCR	368	42(11.4%)	-	6-12	-
Kuwait	[37]	2006-2007 (n=100) 2010-2011 (n=70)	17	< 5	ELISA / RT-PCR	170	14(8.2%)	-	1-12	F
	[38]	2014-2015	16	NM	xTAG GPP/ RT-PCR	109	2(1.8%)	-	-	-
Lebanon	[39]	2010	2	< 10	EIA	79	5 (6%)	-	-	M
	[40]	2011-2013	30	< 5	RT-PCR	739	83(11.2%)	-	12-23	M
Libya		2007-2007	12	< 5	qRT-PCR	520	91 (17.5%)	Summer	6-11	-
Morocco	[42]	2011	12	< 5	ELISA / RT-PCR	335	54 (16.1%)	Summer	12–24	M
Qatar	[43]	2009	5	< 5	qRT-PCR	288	82 (28.4%)	Summar	21-50	-
Tunisia	[44]	2007-2010	36	< 13	RT-PCR	407	38(9.3%)	-	24-60	M
	[45]	2008-2009	12	< 5	RT-PCR	124	11(8.9%)	Autumn and winter	-	M
	[46]	2011-2012	20	<6	qRT-PCR	114	42(36.8%)	winter	-	-

Turkey	[47]	2004-2005	12	< 5	RT-PCR	150	16(10.6%)	-	-	-
	[48]*	2009-2010	NM	< 12	IC	1027	112(10.9%)	winter	1-24	-
	[49]	2012-2013	NM	All age	RT-PCR	427	86 (20.1%)	-	-	-
	[50]	2008-2009	17	< 14	ELISA/ RT-PCR/ qRT-PCR	238	36 (15.1%)	-	12-36	-
Yemen	[51]	2007-2009	15	< 5	ELISA / RT-PCR	290	30 (10%).	-	-	M

Table 2: Proportion of NoV gastroenteritis among patients across all age groups in countries of the Middle East and North Africa.

*Data extracted from abstract; -, not available data; qRT-PCR, quantitative real time reverse transcriptase polymerase chain reaction; EIA, enzyme immunoassays; IC, immunochromatography assay; M, males; F, females.

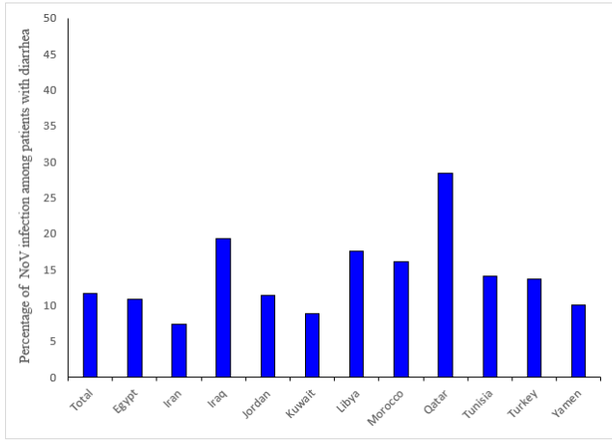

Figure 1: Mean overall proportion of NoV infection among reported acute diarrhea cases by country.

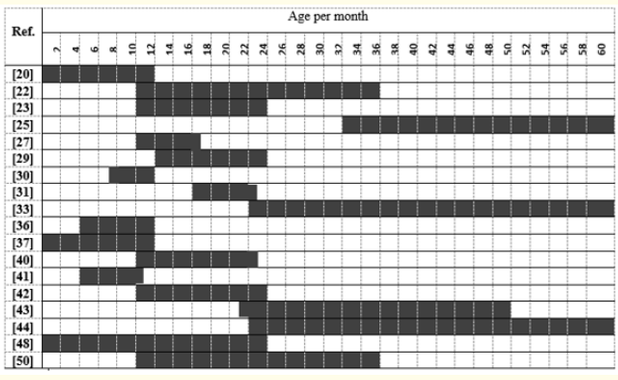

Figure 2: Distribution of NoV infections across all age groups ranged from 1-60 month.

Age and gender distribution of patients with NoV gastroenteritis

In this study, data on the age distribution were available in 18 studies conducted in Egypt [20,22,23], Iran [25,27,29,30], Iraq [31,33], Jordan [36], Kuwait [37], Lebanon [40], Libya [41], Morocco [42], Qatar [43], Tunisia [44], Turkey [48,50]. In these studies, most of NoV infections were found among children during the first two years of life [20,23,27,29,30,31,36,37,40,41,42,48]. Two studies [22,50] reported that the NoV gastroenteritis was occurred by age ranged from 12-36 months whereas some studies stated that the peak distribution of NoV gastroenteritis were observed in age > 24 months [25,33,34,44], as shown in figure 2. On the other hand, 14 studies contained data on the gender distribution from Iran [25,27,28,29,30], Iraq [31,33], Kuwait [37], Lebanon [39,40], Morocco [42], Tunisia [44,45], and yamen [51]. All of the studies, except one study [37], reported that the high prevalence of NoV infection was found in male. The results are summarized in Table 2.

Norovirus Genotype Diversity and Recombinants

Genotype data from 20 studies contained a total of 680 samples from Egypt [21], Iran [24,25,29,30], Iraq [32,33], Jordan [36], Kuwait [37], Lebanon [39,40], Libya [41], Morocco [42], Tunisia [44,45,46], Turkey [47,49,50], and Tunisia [51] were analysed to investigate the most prevalent and widely distributed NoV genotype by RT-PCR. Among these studies, 2 studies [36,42] contained 78 samples subjected for only NoV GII genotypes and the remaining 18 studies contained 602 samples subjected for both NoV GI and NoV GII genotypes. NoV G II strains represented 86% (range 14-90%) of all detected NoVs and GI strains 13.4% (range 0-28). Only two studies contained data on three cases infected with a mixed GI/GII infection [42,51] whereas only one study found GVI in one case [49], as shown in figure 3. Furthermore, 316 of 680 (46.5%) samples from 12 studies [24,30,32,37,42,44,45,46, 47,49,50,51] were subjected for norovirus sequences.

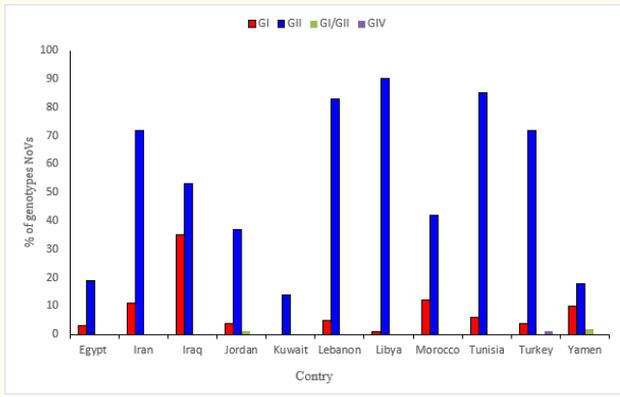

Figure 2: Mean distribution of NoV GI, GII, GIV genotypes using RT-PCR (n=680) by country.

Overall NoV GII.4 was the most detected genotype in the Middle East and North Africa and (165/316 typed NoV; 165/299 typed NoV GII), as well as the most frequently distributed strain in 17 studies. NoV GII.3 was the second most distributed genotype in the region (64/316 typed NoV; 64/299 typed NoV GII), as well as the most frequently identified strain in three studies from Tunisia [44,45,46]. The emergence of a novel GII.21 strain has been found as the predominant cause of gastroenteritis in one study from Turkey [26]. Regarding to NoV GI, NoV GI.3 was the most distributed strain (7/316 typed NoV; 7/17 typed NoV GI) and GI.6 was the second most distributed genotype in the region (6/316 typed NoV; 6/17 typed NoV GI). Other capsid genotypes that showed a wide distribution but relatively low incidence include GI.1, GI.2, GI.4, GII.1, GII.2, GII.5, GII.6, GII.7, GII.8, GII.9, GII.12, GII.13, GII.16, GII.17, GII.21, GII.b, GII.e (Figure 4).

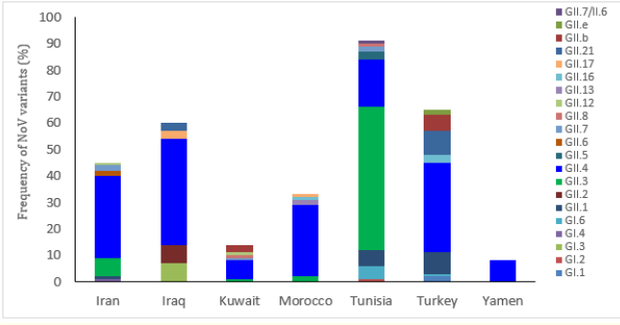

Figure 4: Mean distribution of NoV sequences (n=316) by country.

Clinical features, disease severity, and Intravenous rehydration

Fourteen studies from Middle East and North Africa contained data on clinical manifestations caused by NoV gastroenteritis in the following countries: Egypt [21,23], Iran [24,25,27], Iraq [31], Lebanon [39,40], Libya [41], Morocco [42], Tunisia [48,45], Turkey [49], and Yemen [51]. In most cases, NoV-positive patients suffered from vomiting [21,23,24,25,27,31,39,40,41,42,45,48,49] and Fever [21,23,24,25, 27,31,39, 40,41,51]. Dehydration in several studies, including Iraq [31], Lebanon [39], Morocco [42], Tunisia [45], and Yemen [51] was also reported. Bloody diarrhea due to NoV infection was reported in two studies from Egypt and Tunisia [23,45]. Also, Abdominal pain was reported in studies from Egypt [23], Iran [25,27], Iraq [31], Tunisia [45], Turkey [48], and Yemen [51]. Other symptoms such as watery diarrhea, nausea, headache, myalgia, Chills, and dehydration were reported in some studies [23,25,45,49,48,51]. Disease severity was measured by the vesikari score in four studies with vesikari score ranged from sever, (31.91), Moderate (55.32), and mild (12.77) in Iran [27]; a median severity score (11.8 ± 0.8) in Lebanon [39]; vesikari score ranged from sever (91.6%) and mild to moderate (8.4%) in Lebanon [40]; and vesikari score of 13.12 (P = < 0.0001, vs. 12.38 of non-NoV) in Morocco [42]. The mean (± SD) duration of hospitalization due to NoV diarrhea was 3.9 in one study from Libya [41] whereas the mean (SD) duration in days was 3.7 in Libya [41], 40-43 days in Morocco [42], and 4.3 in Yemen [51]. The treatment of hospitalized children due to NoV infections was reported in three studies by Oral rehydration salts and Intravenous fluids [41,42,51]. No deaths were reported in all included studies.

Discussion

This systematic review provides data on the current status of human NoV across all age groups in the North Africa and Middle East. The extracted data suggest that NoV infection imposes a burden of acute gastroenteritis in the North Africa and Middle East region among children below 5 years old. The detection rate of NoV in the inluded studies ranged between 1.8% and 36.8%. These findings are compatible with data compiled from reports conducted in the Middle East and North Africa and Latin America whereby NoV gastroenteritis rates ranged between 0.82% and 32.9%. [52] and 2.2%-43% [53], respectively.

Of the 32 study included in this meta-analysis, 21 had sufficient data to enable us to estimate of the proportion of positive specimens associated with GI and GII. The results clearly show that norovirus GII.4 is predominantly associated with reports of acute gastroenteritis across all age groups in the North Africa and Middle East region (8 studies out of 12; 66.6%). These findings are in agreement with data from the Africa, Americas, Asia, and Europe [52,54,55] whereby GII.4 is documented to be responsible for about 55-85% of the acute gastroenteritis cases, worldwide. Norovirus GII.4 was responsible for several gastroenteritis pandemics which reported in 1996-1997; 2002; 2004; 2006; 2009; and 2012 [50]. Outbreaks due to GII.4 Sydney strain in winter season during the

2012-2013 was reported globally [51]. The GII.3 strain was the predominant genotype detected in in three studies from Tunisia during 2007-2012 [44,45,46]. Overall, The GII.3 was the second most widely reported of NoV GII strains which in agreement with a previous report on norovirus epidemiology in Africa [56].

The Seasonal Pattern Assessment for norovirus in twenty studies shows the circulation of the norovirus in only three seasons including autumn, winter, and summer where norovirus was commonly detected during autumn and winter seasons as reported by 66.6% (8/12) of the included studies. A recent systematic review reporting the global seasonality of NoV gastroenteritis documented a variable pattern with high incidence during the winter season [57,58]. Factors that could affect on norovirus seasonality include rainfall, temperature, population density, humidity, and human behavior. Reports on murine NoV have observed that low absolute humidity conditions is favourable for virus survival [59].

The ages of the study populations in the included studies varied from <1 year to <15 years (29 studies), up to 18 years (1 study) and in all ages (1 study). The results suggest that children younger than 5 years of age, and particularly children below than 1 year, are very likely to experience NoV gastroenteritis. This observation agrees with several studies in children hospitalized with acute gastroenteritis have showed that NoV infections are widely detected in children below than 2 years of age [60-62].

Oral NoV vaccine candidates are currently in phase I and II trials. Although vaccine cross-protection, effectiveness, and efficacy need to be evaluated in vulnerable populations, it seems possible that a NoV vaccine will be available in the market in the near future. Such a vaccine needs to be designed to induce broad protective immunity due to the large number of circulating serotypes [63].

Conclusion

Although there is no data on NoV in several African countries, the included studies here have provided valuable information on NoVs in low and middle income setting. However, there is very few data on NoV gastroenteritis in both adults and the elderly. Overall, this research has found a high prevalence rate of NoV in children in countries of the North Africa and Middle East. The continuous surveillance of NoV infection among different age groups is very important to estimate the national and regional burden of norovirus gastroenteritis, the viral type diversity, and NoV seasonality. This knowledge is important to support intervention strategies and prevention of NoV in the region.

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